Rates and Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Substance-Induced Psychosis

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Objective: The authors investigated the rates of conversion to schizophrenia and bipolar disorder after a substance-induced psychosis, as well as risk factors for conversion.

Method: All patient information was extracted from the Danish Civil Registration System and the Psychiatric Central Research Register. The study population included all persons who received a diagnosis of substance-induced psychosis between 1994 and 2014 (N=6,788); patients were followed until first occurrence of schizophrenia or bipolar disorder or until death, emigration, or August 2014. The Kaplan-Meier method was used to obtain cumulative probabilities for the conversion from a substance-induced psychosis to schizophrenia or bipolar disorder. Cox proportional hazards regression models were used to calculate hazard ratios for all covariates.

Results: Overall, 32.2% (95% CI=29.7–34.9) of patients with a substance-induced psychosis converted to either bipolar or schizophrenia-spectrum disorders. The highest conversion rate was found for cannabis-induced psychosis, with 47.4% (95% CI=42.7–52.3) converting to either schizophrenia or bipolar disorder. Young age was associated with a higher risk of converting to schizophrenia. Self-harm after a substance-induced psychosis was significantly linked to a higher risk of converting to both schizophrenia and bipolar disorder. Half the cases of conversion to schizophrenia occurred within 3.1 years after a substance-induced psychosis, and half the cases of conversion to bipolar disorder occurred within 4.4 years.

Conclusions: Substance-induced psychosis is strongly associated with the development of severe mental illness, and a long follow-up period is needed to identify the majority of cases.

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The prevalence of substance abuse is higher among persons with mental illness than in the general population (1). The reasons for this are unclear, but many possible links have been proposed. A common hypothesis is that psychiatric patients use substances of abuse as a way of self-medicating. It has also been suggested that the use of cannabis can speed up the process of developing schizophrenia in vulnerable individuals and that there may be a dose-response association (2–5). Less is known about the link between the use of other substances of abuse and the development of schizophrenia or other psychiatric diagnoses.

Some substances themselves can cause psychosis. A substance-induced psychosis is a psychotic state occurring during intoxication or withdrawal and lasting at least 48 hours. New findings suggest that a large number of patients with a substance-induced psychosis later develop chronic psychotic conditions. It appears that cannabis-induced psychosis converts to schizophrenia in up to 50% of cases (6, 7). Because this percentage is high, some studies have set out to examine whether the diagnosis of cannabis-induced psychosis is distinguishable from schizophrenia combined with cannabis use. One study (8) showed that patients with a substance-induced psychosis more often had a family history of substance abuse and were diagnosed at an older age compared with patients with a primary psychosis. Not much is known about how psychoses induced by other substances may predict long-term chronic psychotic illness. Other types of substance-induced psychosis appear to have lower rates of conversion to schizophrenia—around 30% for amphetamines, 24% for hallucinogens, 21% for opioids, and 5% for alcohol (9). Another study showed that 23% of patients with substance-induced psychosis are diagnosed with schizophrenia within 3 years of follow-up (10).

Psychiatric patients who also have a substance abuse problem are often diagnosed later than those with no substance abuse, and consequently treatment is delayed (1). It would be of great interest to identify those at high risk so that treatment could be initiated earlier.

The aims of this study were to identify the proportion of patients diagnosed with substance-induced psychosis who

later develop schizophrenia or bipolar disorder and to identify risk factors for conversion to schizophrenia or bipolar disorder following a substance-induced psychosis.

METHOD

Register

All patient information was extracted from the Danish Civil Registration System, which includes all persons born in Denmark or with permanent residence in Denmark (11). The civil registration number is used to identify individuals in all national registers, enabling accurate linkage. Our data are from the nationwide Psychiatric Central Research Register (12), which has registered all inpatient psychiatric treatment since 1969 and outpatient treatment since 1995. Prior to 1994, codes were assigned using ICD-8, and then the register switched directly to ICD-10.

Population

The study population included all persons who received a diagnosis of substance-induced psychosis between 1994 and 2014. Patients who had a previous diagnosis of schizophrenia spectrum or bipolar disorders were excluded.

The ICD-10 codes used to determine the study population were substance-induced psychosis induced by alcohol (F10.5), opioids (F11.5), cannabis (F12.5), sedatives (F13.5), cocaine (F14.5), amphetamines (F15.5), hallucinogens (F16.5), and mixed/other (F18.5, F19.5, and patients given two or more of the F10.5–F16.5 diagnoses simultaneously). Ten comparison subjects were selected for each case subject, matched on sex, year and month of birth, and calendar time, i.e., being alive at the date of the incident substance-induced psychosis of the corresponding case subject (match date). Rates of conversion to schizophrenia or bipolar disorder were then, for the comparison subjects, estimated after this match date. Comparison subjects who had diagnoses of schizophrenia spectrum or bipolar disorders prior to this match date were excluded.

Outcomes and Predictors

The diagnostic codes used to determine the outcomes were ICD-10 F20.x and ICD-8 295 for schizophrenia and ICD-10 F31 and ICD-8 269x for bipolar disorder. The following predictors of conversion were examined, selected because they would be easily accessible to clinicians: self-harm (ICD-10 codes X6–X84 and ICD-8 codes E950–E959; established using both the Psychiatric Central Research Register and the National Patient Register [13]), substance use disorders (ICD-8 codes 291.1, 303.x, and 304.x and ICD-10 codes F1x.x except F1x.5), attention deficit hyperactivity disorder (ADHD) (ICD-10 codes F90.x), personality disorders (ICD-8 codes 301.x and ICD-10 codes F60.x and F61.x), anxiety disorders (ICD-8 codes 300.0 and 300.2 and ICD-10 codes F40.x and F41.x), unipolar depression (ICD-8 code 296.2 and ICD-10 codes F32.x and F33.x), eating disorders (ICD-8 codes 784.0 and ICD-10 codes F50.x), and autism (ICD-10 codes F84.x except F84.2).

Statistical Analysis

The case subjects were followed up from incident substance-induced psychosis, and comparison subjects from their corresponding match date, until the first occurrence of schizophrenia or bipolar disorder or until death, migration, or Aug. 14, 2014, whichever came first. The Kaplan-Meier method was used to obtain cumulative probabilities for the conversion from a substance-induced psychosis to schizophrenia or bipolar disorder and for subsequent self-harm. The first set of analyses used Cox proportional hazards regression models to estimate hazard ratios for conversion of cases with substance-induced psychosis relative to comparison subjects. These analyses incorporated information on the individually matched strata, making them automatically adjusted for all matching variables. The next set of analyses used Cox proportional hazards regression among cases with substance-induced psychosis to identify predictors of later conversion. Self-harm was assessed as a risk factor split into whether it had occurred before or at any time after the substance-induced psychosis, in the latter case as a time-varying covariate. Analyses were adjusted for age and sex.

RESULTS

The study population consisted of 6,788 patients who received an incident diagnosis of substance-induced psychosis over a 20-year period and who did not have any previous record of treatment for schizophrenia spectrum disorders or bipolar disorder. After exclusion of comparison subjects with previous psychosis or bipolar disorder, the patients were matched to 67,227 comparison subjects. Twenty-seven patients (0.4%) were each matched to eight comparison subjects, 599 patients (8.8%) were each matched to nine comparison subjects, and the remaining 90.8% were each matched to 10 comparison subjects. Table 1 lists the distributions of substances and previous diagnoses among patients with substance-induced psychosis. Alcohol induced 34% of the psychoses, cannabis 22%, and mixed/other substances 27%. The age at onset varied by type of substance, with cannabis, cocaine, amphetamines, hallucinogens, and other substances inducing psychosis at mean ages of 30 or less and alcohol, opioids, and sedatives inducing psychosis at mean ages above 45.

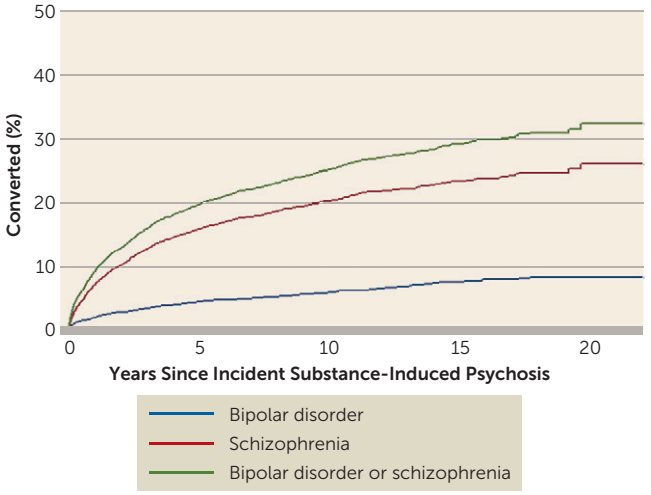
Proportion of Patients Converting to Psychotic Conditions

The 20-year conversion rate to either schizophrenia or bipolar disorder for patients with a substance-induced psychosis was 32.2% (95% CI=29.7–34.9) (Figure 1). The conversion rates were 26.0% (95% CI=23.7−28.9) for schizophrenia and 8.4% (95% CI=7.4−9.5) for bipolar disorder. Figure 2 shows substance-specific conversion rates to either schizophrenia or bipolar disorder, with the highest conversion rate, 41.2% (95% CI=36.6−46.2), observed for cannabis-induced psychosis converting to schizophrenia. Combining the two outcomes, 47.4% (95% CI=42.7−52.3) of

TABLE 1. Diagnoses of Patients With Incident Substance-Induced Psychosis in a Registry Study of Conversion to Schizophrenia and Bipolar Disorder

	Men		Women		All	
Substance and Earlier Diagnoses	N	%	N	%	N	%
Substance-induced psychosis	5,078	74.8	1,710	25.2	6,788	100.0
Alcohol	1,680	33.8	635	37.1	2,315	34.1
Opioids	88	1.7	70	4.1	158	2.3
Cannabis	1,222	24.1	270	15.8	1,492	22.0
Sedatives	33	0.7	87	5.1	120	1.8
Cocaine	136	2.7	34	2.0	170	2.5
Amphetamines	423	8.3	132	7.7	555	8.2
Hallucinogens	91	1.8	23	1.4	114	1.7
Mixed or other substances	1,405	27.7	459	26.8	1,864	27.5
Earlier diagnoses						
Substance use disorder	759	44.4	2,179	42.9	2,938	43.3
Attention deficit hyperactivity disorder	154	3.0	28	1.6	182	2.7
Personality disorder	831	16.4	464	27.1	1,296	19.1
Unipolar depression	426	8.4	262	15.3	688	10.1
Anxiety disorder	210	4.1	144	8.4	354	5.2
Autism	25	0.5	3	0.2	28	0.4
Eating disorder	4	0.1	43	2.5	47	0.7
Self-harm before psychosis	1,165	22.9	592	34.6	1,757	25.9

FIGURE 1. Rates of Conversion to Schizophrenia and Bipolar Disorder Following Incident Substance-Induced Psychosis in a Registry Study (N=6,788)



patients with a cannabis-induced psychosis later converted to either schizophrenia or bipolar disorder. This was the highest incidence for any substance. The rates for the other substances were 27.8% (95% CI=19.5–38.6) for patients with a hallucinogen-induced psychosis, 35.0% (95% CI=31.8–38.3) for patients with a psychosis induced by mixed/other substances, 32.3% (95% CI=26.0–39.7) for those with an amphetamine-induced psychosis, 20.2% (95% CI=13.7–29.3) for those with a cocaine-induced psychosis, 19.9% (95% CI=12.8–30.1) for those with a sedative-induced psychosis, 20.9% (95% CI=11.9–35.1) for those with an opioid-induced psychosis, and 22.1% (95% CI=17.6–27.5) for those with an alcohol-induced psychosis.

Risk of Conversion in Case Subjects Relative to Comparison Subjects

Table 2 lists hazard ratios for conversion to schizophrenia or bipolar disorder for persons with substance-induced psychosis relative to comparison subjects. The hazard ratio for conversion to schizophrenia was 77.3 (95% CI=65.2–91.7). The highest risk was observed for cannabis-induced psychosis, with a hazard ratio of 101.7 (95% CI=74.1–139.7). The remaining types of substance-induced psychoses were associated with hazard ratios ranging from 23.4 (95% CI=8.2–66.5) for opioid-induced psychosis to 79.3 (95% CI=43.5–144.5) for amphetamine-induced psychosis.

The hazard ratio for conversion to bipolar disorder was 24.4 (95% CI=20.1–29.6) for persons with substance-induced psychosis relative to comparison subjects. Given the broad confidence intervals for individual substances, there were no indications of any type of substance being more strongly associated with conversion to bipolar disorder than others.

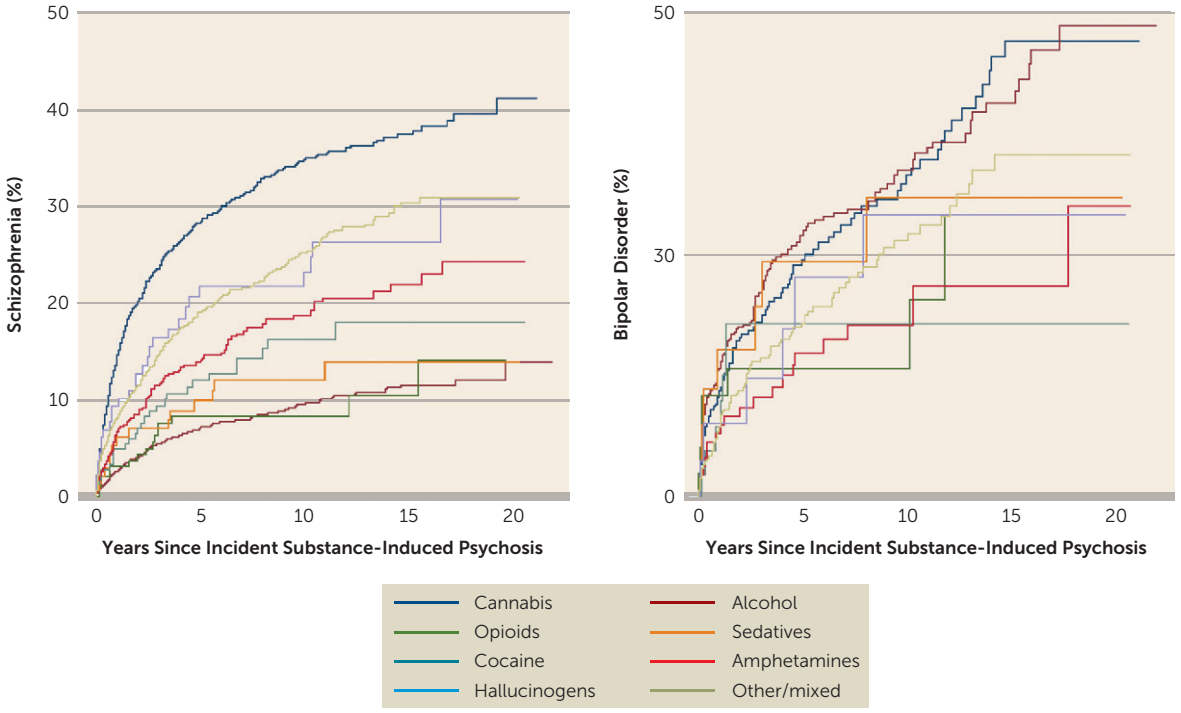
Figures 1 and 2 plot the overall conversion rates for schizophrenia and bipolar disorder and the rates for each substance category. We found that 50% of conversions to schizophrenia occurred within 3.1 years, and 50% of conversions to bipolar disorder occurred within 4.4 years. For schizophrenia, 50% of the male patients with a cannabis-induced psychosis converted within 2.0 years and 50% of the female patients converted within 4.4 years.

Predictors of Conversion

Predictors of conversion to schizophrenia or bipolar disorder following a substance-induced psychosis are listed in Table 3. For conversion to schizophrenia, the risk decreased with increasing age at incident substance-induced psychosis. No such pattern was seen for conversion to bipolar disorder.

Substance use disorder (hazard ratio=1.19, 95% CI=1.05–1.37), personality disorders (hazard ratio=1.29, 95% CI=1.09–1.52), and eating disorders (hazard ratio=1.73, 95% CI=1.05–2.87) were significantly linked to conversion from a substance-induced psychosis to schizophrenia. Among persons with substance-induced psychosis, conversion to bipolar disorder was statistically significantly predicted by preceding diagnoses of personality disorders (hazard ratio=1.46, 95% CI=1.13–1.89), unipolar depression (hazard ratio=2.03, 95% CI=1.54–2.67), and anxiety disorders (hazard ratio=1.59, 95% CI=1.11–2.27). A previous episode of self-harm was associated with a reduced risk of converting to schizophrenia (hazard ratio=0.80, 95% CI=0.68–0.95) but not to bipolar disorder (p=0.71). Conversely, self-harm after a substance-induced psychosis was associated with a higher risk of conversion to schizophrenia and bipolar disorder, with hazard ratios of 1.92 (95% CI=1.58–2.34) and 1.60 (95% CI=1.13–2.27), respectively.

FIGURE 2. Rates of Conversion to Schizophrenia and Bipolar Disorder Following Incident Substance-Induced Psychosis, by Substance, in a Registry Study (N=6,788)



Interaction analyses did not reveal tendencies toward different risk factors for conversion among the different types of substance-induced psychoses (data not shown).

DISCUSSION

We found that 32.2% of patients with a substance-induced psychosis later converted to either bipolar disorder or schizophrenia. The highest conversion rate (47.4%) was found for cannabis-induced psychosis. Young age was associated with a higher risk of conversion to schizophrenia; the risk was highest for those in the range of 16–25 years. Self-harm after a substance-induced psychosis was significantly linked to a higher risk of converting to both schizophrenia and bipolar disorder.

About half the cases that converted to schizophrenia did so within the first 3 years after a substance-induced psychosis, and about half the cases that converted to bipolar disorder did so within the first 5 years.

Substance-Induced Psychosis as a Risk Factor

The most common form of substance-induced psychosis in our study was alcohol-induced psychosis, for which the rate of conversion to more severe psychotic diagnoses was 22.1%. The second largest group consisted of psychosis induced by mixed/other substance use, with a conversion rate of 35.0%. The third largest group was cannabis-induced psychosis, which had the highest conversion rate, at 47.4%. The remaining substances all made up small percentages of substance-induced psychoses. This distribution reflects the overall use of substances in the general population, with alcohol and cannabis being the most commonly used. The reason the mixed-substance group was so large could be that it consisted of combinations of all substances, and many substance users take multiple substances at the same time (14). All types of substance-induced psychosis were associated with large increases in risk of conversion to schizophrenia and bipolar disorder compared with comparison subjects.

Cannabis and Schizophrenia

Studies have shown that cannabis use and cannabis-induced psychosis increased the risk of schizophrenia and caused an earlier onset of schizophrenia (4, 6, 7). This corresponds with our finding that 47.4% of patients with cannabis-induced psychosis converted to schizophrenia and that this rate corresponds to almost twice the risk of conversion compared with substance-induced psychoses that were not induced by cannabis. This is in line with findings from another recent registry-based study (15) in which, among substance use variables, only cannabis use predicted schizophrenia. Because of the high conversion rate also shown in other studies, it has been suggested that cannabis-induced psychosis is not distinguishable from the onset of schizophrenia. Various possible reasons have been suggested for the elevated incidence of schizophrenia among cannabis users. One is that the initial diagnosis of substance-induced psychosis is in reality the onset of schizophrenia, but the heavy consumption of substances in this group of patients leads to faulty diagnosis. Another is that a substance-induced psychosis may be a step on the way to developing a primary psychosis—and therefore it could be used as a marker. Studies have

TABLE 2. Risk of Conversion to Schizophrenia and Bipolar Disorder Among Patients With Incident Substance-Induced Psychosis Relative to Matched Comparison Subjects in a Registry Study

	Schizophrenia				Bipolar Disorder			
Group	N	Hazard Ratio	95% CI	p	N	Hazard Ratio	95% CI	p
Comparison subjects	200	1 (ref.)			188	1 (ref.)		
Patients with substance-induced psychosis that later converted	1,174	77.3	65.2–91.7	<0.001	361	24.4	20.1–29.6	<0.001
Substance inducing the psychosis								
Alcohol	183	74.0	48.4–113.3	<0.001	144	28.4	20.6–39.3	<0.001
Opioids	12	23.4	8.2–66.5	<0.001	7	13.6	4.3–43.0	<0.001
Cannabis	433	101.7	74.1–139.7	<0.001	90	32.5	21.1–50.0	<0.001
Sedatives[a]	13				7	33.0	6.9–159.0	<0.001
Cocaine	22	43.0	16.3–113.6	<0.001	5	12.2	3.3–45.5	<0.001
Amphetamines	97	79.3	43.5–144.5	<0.001	20	17.4	8.3–36.4	<0.001
Hallucinogens	23	56.2	19.4–162.5	<0.001	6	20.0	5.0–80.0	<0.001
Mixed or other substances	391	67.2	50.9–88.8	<0.001	82	18.7	12.9–27.0	<0.001

[a] Hazard ratio for schizophrenia not computed.

shown that these are two separable diagnoses, and the high conversion rate is not caused by faulty diagnosis but suggests that cannabis-induced psychosis is a step on the way to schizophrenia (8, 16–18).

In our study, 50% of conversions to schizophrenia occurred within 3.1 years, but the remaining 50% continued to convert more evenly over many years, suggesting distinct, separate diagnoses. If the majority of cannabis-induced psychosis cases were actually misdiagnosed onset of schizophrenia, the conversions would not occur over such a long period of time. The conversion rate was higher for cannabis-induced psychosis compared with other substances, although in many cases this difference was not statistically significant because of wide confidence intervals around the estimates. This supports the theory that cannabis use can dispose a vulnerable subgroup in the population to schizophrenia, or speed up the debut of the disease (2, 3). The theory that there is a specific link between cannabis and schizophrenia is further supported by evidence of a dose-response relationship between the consumption of cannabis and the risk of schizophrenia (19–21). Cannabis-induced psychosis must therefore be considered an important risk factor for the development of schizophrenia.

Conversion to Bipolar Disorder

Psychoses induced by alcohol, cannabis, or sedatives were the disorders most strongly at increased risk of conversion to bipolar disorder relative to comparison subjects. We found that 9.9% of patients with an alcohol-induced psychosis later converted to bipolar disorder. This rate is higher than in previous studies, in which only about 5% convert. Although the conversion to bipolar disorder in the substance-induced psychosis population is much less frequent than conversion to schizophrenia, alcohol-induced psychosis converts to bipolar disorder almost as often as to schizophrenia. We found that among cases of alcohol-induced psychoses, 9.9% converted to bipolar disorder and 13.9% to schizophrenia. This may explain why the high conversion rate after a substance-induced psychosis has not previously been shown, as other studies have not looked directly at alcohol-induced psychoses. The category of bipolar disorder in our study may have included some patients whose symptoms had never included full mania but only hypomania, corresponding to the DSM-5 diagnosis of bipolar II disorder. Excluding the corresponding ICD-10 diagnosis (F31.0: bipolar disorder, current episode hypomanic) had almost no influence on conversion rates or hazard ratios (data not shown).

Risk Factors for Conversion

Among patients with a substance-induced psychosis, the age group with the highest risk of converting to schizophrenia were those in the range of 16–25 years, and the age group at lowest risk were those age 51 and older. This supports the idea that young people are at especially high risk of converting to schizophrenia. For conversion to bipolar disorder, the age distribution was more even, and the age group at highest risk of conversion were those age 51 and older. This suggests that all patients, regardless of age, could benefit from a follow-up period of continued monitoring.

Men had a higher risk of converting to schizophrenia—a gender distribution resembling that of schizophrenia in the general population (22). The opposite was shown regarding conversion to bipolar disorder, where men were at a lower risk, which does not reflect the gender distribution of bipolar disorder in the general population (23). This, combined with the faster conversion to bipolar disorder for female patients, suggests that women have an especially high risk of conversion compared with men after a substance-induced psychosis.

A majority of patients with schizophrenia or bipolar disorder have a psychiatric history preceding these diagnoses. It has been suggested that schizophrenia or bipolar disorder could be preceded by other comorbid disorders, such as ADHD, personality disorders, unipolar depression, anxiety disorders, autism, and eating disorders (24–26). In this study

TABLE 3. Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Incident Substance-Induced Psychosis in a Registry Study

	Schizophrenia				Bipolar disorder			
Variable	Converted (N)	Hazard Ratio	95% CI	p	Converted (N)	Hazard Ratio	95% CI	p
Substance inducing the psychosis								
Alcohol	183	1 (ref.)			144	1 (ref.)		
Opioids	12	0.78	0.43–1.40	0.40	7	0.72	0.34–1.55	0.41
Cannabis	433	2.17	1.77–2.66	<0.001	90	1.49	1.07–2.08	0.02
Sedatives	13	1.94	1.10–3.42	0.02	7	0.67	0.31–1.44	0.30
Cocaine	22	0.84	0.54–1.33	0.47	5	0.70	0.28–1.76	0.45
Amphetamines	97	1.23	0.94–1.61	0.12	20	0.83	0.50–1.37	0.46
Hallucinogens	23	1.28	0.82–1.98	0.28	6	1.24	0.53–2.87	0.62
Mixed or other substances	391	1.48	1.21–1.81	<0.001	82	0.93	0.68–1.27	0.65
Earlier diagnoses								
Substance use disorder	467	1.19	1.05–1.37	0.009	191	1.08	0.85–1.38	0.52
Attention deficit hyperactivity disorder	31	1.02	0.71–1.46	0.93	7	1.27	0.59–2.74	0.54
Personality disorder	229	1.29	1.09–1.52	0.002	115	1.46	1.13–1.89	0.004
Unipolar depression	106	1.10	0.89–1.36	0.36	77	2.03	1.54–2.67	<0.001
Anxiety disorder	45	0.95	0.70–1.29	0.73	38	1.59	1.11–2.27	0.01
Autism	≤4[a]	0.41	0.13–1.27	0.12	≤4[a]	1.04	0.14–7.64	0.97
Eating disorder	17	1.73	1.05–2.87	0.03	≤4[a]	0.75	0.27–2.07	0.58
Self-harm before substance-induced psychosis	177	0.80	0.68–0.95	0.01	80	0.95	0.72–1.24	0.71
Self-harm after substance-induced psychosis	124	1.92	1.58–2.34	<0.001	40	1.60	1.13–2.27	0.008
Age at incident substance-induced psychosis (years)								
≤15	11	0.36	0.20–0.66	0.001	0			
16–25	639	1 (ref.)			103	1 (ref.)		
26–30	179	0.74	0.63–0.88	0.001	38	0.99	0.68–1.44	0.96
31–35	119	0.59	0.48–0.73	<0.001	30	0.87	0.57–1.32	0.51
36–40	99	0.60	0.47–0.75	<0.001	32	1.05	0.68–1.61	0.82
41–50	102	0.32	0.25–0.40	<0.001	71	1.14	0.79–1.64	0.48
≥51	29	0.12	0.08–0.18	<0.001	87	1.69	1.16–2.44	0.006
Male	980	1.58	1.35–1.86	<0.001	228	0.68	0.54–0.85	0.001

[a] Danish laws regarding data protection do not allow reporting of cell counts <4 but >0.

we tried to identify subgroups of patients with substance-induced psychosis who might be at higher risk of converting to a chronic psychotic condition. We found a significantly higher risk of converting to schizophrenia in patients who had a preexisting substance use disorder, personality disorder, or eating disorder. We found that patients with a preexisting diagnosis of an anxiety disorder, unipolar depression, or a personality disorder all had a higher risk of converting to bipolar disorder. The finding of eating disorders is interesting, as the clinical presentation of eating disorders often includes psychotic features relating to self-image. Our results could thus indicate a potential interplay in which these psychotic symptoms may be precursors of a disorder such as schizophrenia.

Patients with schizophrenia or bipolar disorder have been shown to be at high risk of suicidal ideation and self-harm, as are patients with substance abuse (27–30). We found that self-harm after a substance-induced psychosis was associated with an increased risk of conversion to both schizophrenia and bipolar disorder. This is an important finding because self-harm is already known to be one of the biggest risk factors for repeated self-harm and/or suicide (31–34). This means that a subpopulation of patients who have had a substance-induced psychosis and later present with a self-harm attempt are especially vulnerable and at high risk of developing schizophrenia or bipolar disorder. In their case, follow-up after a substance-induced psychosis could also help prevent attempts at self-harm or suicide.

Implications

We are not aware of any international guidelines concerning follow-up of patients after a substance-induced psychosis, and it is likely that many countries and health systems do not have follow-up policies or programs in place. The main reason for this could be that symptoms of a substance-induced psychosis, by definition, wear off when the patient is no longer under the influence of, or suffering symptoms of withdrawal from, the substance involved. Our findings suggest that a large group of these patients are at high risk of developing schizophrenia or bipolar disorder, and that many of them go

on to do self-harm. It is important to diagnose new cases of schizophrenia and bipolar disorder as soon as possible and to initiate treatment without delay, because prolonged psychosis without treatment is associated with a worse prognosis (35). Life expectancy is lower for psychiatric patients and for persons with substance abuse, and even more so for the group that suffers both (36, 37). Psychiatric patients with substance abuse especially are often diagnosed later than those without substance abuse (1). The early detection of schizophrenia and bipolar disorder among substance abusers who experience a substance-induced psychosis could prevent some of the delay in diagnosis that occurs in substance abusers.

We wanted to develop a risk profile that could identify patients at a higher risk and help early detection of these cases. Based on the different risk factors identified in different analyses and the overall conversion rate of 32.2%, it seems most reasonable to suggest that all patients with a substance-induced psychosis should be offered follow-up. Since only 50% of the cases that convert from cannabis-induced psychosis to schizophrenia do so within the first 2 years, and the rate of conversions over time is lower for all other substances and for conversion to other diagnoses, the follow-up period should be at least 2 years. An extended follow-up might also help prevent incidents of self-harm. Our findings suggest that patients who present with self-harm and have previously had a substance-induced psychosis are at even higher risk of converting to schizophrenia or bipolar disorder. In Denmark patients are offered follow-up after self-harm, but not after a substance-induced psychosis.

Strengths and Limitations

Because our study is a register-based cohort study, all our findings can be reproduced. However, because it was based on diagnoses from registers, we could not validate the diagnoses, which may be a problem given the similarity between cannabis-induced psychosis and schizophrenia and may explain some of the high conversion rates. We have discussed the merit of the cannabis-induced psychosis entity, and we believe this similarity does not account for the high conversion rate. It is possible that a bias exists in which diagnosing a psychosis as secondary to substance use may be seen as preferable to diagnosing a primary psychotic disorder such as schizophrenia. However, since the conversions continue at a steady pace over a period of many years, it appears unlikely that the high conversion rates are predominantly due to original misdiagnosis of the psychotic disorder as secondary rather than primary.

Only cases of substance-induced psychosis that lead to psychiatric treatment are registered in the system and were a part of this study. Studies have shown that cannabis often can induce short-term psychotic symptoms in the general population (5, 38). These patients may not seek medical attention, and factors such as patient attitudes, socioeconomic status, and the like may influence the probability of receiving treatment for a substance-induced psychosis. It is likely, however, that all the more severe cases receive treatment. Therefore, our results may not be generalizable for all cases of substance-induced psychosis. In a register-based study, it is not possible to obtain information about substance use, the amounts involved, and continued use after a substance-induced psychosis. Therefore, it cannot be determined whether it is a substance-induced psychosis or prolonged exposure to substances that is related to the development of schizophrenia or bipolar disorder. A final limitation lies in the fact that the registers do not allow us to ascertain whether conversion rates differed depending on whether patients continued using the substances after the substance-induced psychosis.

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