Long-term follow-up of patients treated for psychotic symptoms that persist after stopping illicit drug use

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Background: The long-term outcome of patients diagnosed with drug-induced psychotic disorders in China is unknown.

Aim: Assess the course of illness and severity of psychiatric symptoms in patients previously admitted to a psychiatric hospital for treatment of psychotic symptoms that were induced by the use of illicit drugs.

Methods: Patients with psychotic symptoms at the time of their first psychiatric admission who had used illicit drugs in the month prior to admission were followed up 13 to 108 months after admission. Patients and coresident family members were interviewed about post-discharge drug use and psychotic symptoms.

Results: The 258 identified patients were primarily young, unemployed males whose most common drug of abuse was methamphetamines and who had been abusing drugs for an average of 7 years at the time of admission. Among these patients 189 (73%) were located and reinterviewed; 168 (89%) had restarted illicit drug use and 25 (13%) had required rehospitalization over the follow-up period. In 114 patients (60%) the psychotic symptoms resolved in less than 1 month after stopping the drugs, in 56 (30%) the symptoms persisted for 1 to 6 months, and in 19 (10%) the symptoms persisted for longer than 6 months (in 8 of these the diagnosis had changed to schizophrenia). Compared to the other two groups, patients whose symptoms persisted more than 6 months were more likely to have a family history of mental illness, an earlier age of onset and a longer duration of drug abuse prior to the index admission; they were also more likely to have been re-hospitalized during the follow-up period and to have psychotic symptoms at the time of follow-up.

Conclusion: Most patients with substance-induced psychotic disorders in our sample had a good long-term prognosis but those who started illegal drug use early, used drugs for prolonged periods, or had a family history of psychiatric illnesses were more likely to develop a chronic psychosis. Further prospective studies are needed to determine the relationship of the neurotoxic effects of illicit drugs and the predisposing characteristics of the individuals in the development of chronic psychosis in persons who use illicit drugs.

1. Introduction

The clinical symptoms of patients given the diagnosis of ‘psychoactive substance-induced psychotic disorder’ are mainly positive psychotic symptoms such as hallucinations and delusions.[1,2] Studies from outside of China find that many individuals diagnosed with the diagnosis develop residual psychotic symptoms[3,4] that impair their social and occupational functioning. But the pattern of illegal substance use in China is quite different from that in high-income countries[5] so the prognosis of this diagnosis may also be different. There are, however, no studies in China that assess long-term outcomes of patients with this diagnosis. The current study aims to identify the long-term outcomes of individuals in China who required psychiatric hospitalization to manage psychotic symptoms that were induced by the use of illicit drugs.

2. Methods

2.1 Identification of participants

The identification and follow-up of patients is shown in Figure 1. Patients discharged from the Shenzhen Kangning Hospital between January 2003 and December 2010 with a discharge diagnosis of ‘psychiatric disorder induced by a psychoactive substance’ (based on the Chinese Classification and Diagnostic Criteria of Mental Disorders, CCMD-3[6]), who had psychotic symptoms at the time of admission that were induced by illicit drug use in the month prior to admission, who did not have a co-morbid diagnosis of schizophrenia or a serious physical illness, and who had no prior psychiatric hospitalizations were followed up 13 to 108 months after the index admission (median follow-up time was 49 months; the 25%-75% interquartile range was 34 to
Among the 258 discharged patients who met the inclusion criteria, 189 (73.3%) were located and agreed to participate in the follow-up survey. Either the patient or the patient’s legal guardian signed an informed consent to participate. The study was approved by the Ethics Committee of the Shenzhen Kangning Hospital.

### 2.2 Assessments

The two-part follow-up survey was conducted between January and March 2012. The initial interview collected information about the patients’ demographic characteristics, drug history (age of onset, duration of use, type of drug used, etc.) and psychiatric history. 111 of the 189 subjects reported this information in face-to-face interviews and 78 subjects provided the information over the phone. There were no differences in gender or age between subjects who participated in the two types of interviews. A subsequent face-to-face evaluation of all subjects by one of the two participating research psychiatrists involved administration of 14 items from the Positive and Negative Syndrome Scale (PANSS)\(^7\)—the 7 items about positive symptoms and the 7 items about negative symptoms—to assess the presence and severity of positive and negative psychotic symptoms at the time of the follow-up and (retrospectively) at the time of the index admission, at one month after the index admission, and at six months after the index admission. Each of the items is rated on a 7-point Likert scale with higher scores representing more severe pathology. The two participating psychiatrists had good inter-rater reliability for the 14 PANSS items assessed: When simultaneously assessing 97 subjects the Pearson’s correlation coefficient for the total score for the 14 items was 0.72. In all cases the information was initially obtained from the subject and then verified by asking a coresident family member. If the information provided by the patient and the family member was contradictory the information provided by the family member was considered more accurate.

### 2.3 Determination of the persistence of psychotic symptoms

Patients were classified into three groups based on the reported persistence of psychotic symptoms after the index admission. For the purpose of this study if any of the 14 PANSS items assessed were coded as 4 (moderate) or higher or if any two items were coded as 3 (mild) ‘clinically significant’ psychotic symptoms were considered present. Subjects who reported no reinitiation of illicit drug use in the six months following the index admission and whose retrospective report of symptoms indicated that no clinically significant psychotic symptoms were present 1 month after the index admission were classified as having psychotic symptoms for less than 1 month. Those who had clinically significant psychotic symptoms at 1 month after
admission but not at 6 months after admission (without intervening reinitiation of illicit drug use) were classified as having psychotic symptoms for 1 to 6 months. And those who reported having clinically significant psychotic symptoms 6 months after admission (without intervening reinitiation of illicit drug use) were classified as having psychotic symptoms persisting for greater than 6 months. For individuals who had reinitiated illicit drug use in the 6 months after admission the classification was based on the timing of the first remission of the psychotic symptoms after the index admission (not on the status at 1 month and 6 months after admission): if the remission occurred within 1 month of admission the patient was classified as having psychotic symptoms for less than one month; if the remission occurred 1 to 6 months after admission they were classified as having psychotic symptoms for 1 to 6 months.

2.4 Statistical methods

Comparison of the characteristics of subjects who had a single drug of abuse at the time of admission to those who had multiple drugs of abuse and comparison of those who did and did not complete the follow-up assessment used chi-square tests and t-tests. The characteristics of the three groups of patients classified according to persistence of psychotic symptoms were compared using chi-square tests for categorical variables and F-tests for continuous variables. If significantly different, multiple comparison tests were used to identify which of the three groups were significantly different. Two-tailed significance was set at \( \alpha=0.05 \). SPSS 13.0 software was used for the analysis.

3. Results

3.1 Characteristics of psychiatric inpatients with psychotic symptoms induced by illicit drug use

The characteristics of the 258 identified subjects are shown in Table 1. They were primarily young, unemployed males whose most common drug of abuse was methamphetamine and who had been abusing drugs for several years. Among these subjects, 77 (29.8%) had primarily used a single illicit drug prior to admission and 181 (70.2%) had used multiple illicit drugs. As shown in the table, compared to those who used a single drug, those who used multiple illicit drugs were older and had a longer duration of drug use, but there were no differences between the groups in the age of onset of drug use, in the main illicit drug used in the month prior to admission or in the severity of positive or negative psychotic symptoms at the time of admission.

3.2 Recidivism and rehospitalization rates in patients who were followed up

Of the 258 patients who met inclusion criteria, 189 (73.3%) were located and agreed to participate in the follow-up assessment. There were no significant differences between those who did and did not participate in the follow-up assessment by gender, age, age of onset of drug use, duration of drug use, or type of illicit drug use. However, the 69 subjects that were not followed up had a much shorter mean (sd) duration of education (5.5 [4.6] years) than that of the 189 who did participate in the follow-up (8.1 [4.0] years; t-test=17.24, p<0.001).

As shown in Table 2, there was a very high recidivism rate of 89% (168/189) over the follow-up period. In the month prior to follow-up 21 (11.1%) of the patients had taken illicit drugs; among them 13 (61.9%) had clinically significant psychotic symptoms at the time of follow-up. In the six months prior to follow-up 32 (16.9%) patients had used illicit drugs and 15 (46.9%) of them had significant symptoms at follow-up. During the follow-up period 15 of the 189 patients had one additional psychiatric hospitalization, 6 had two additional hospitalizations, and 4 had four or five additional hospitalizations.

3.3 Comparison of patients whose psychotic symptoms persisted for <1 month, 1-6 months and >6 months after stopping illicit drug use

Among the 189 patients who were followed up after hospital discharge, retrospective assessment of the duration of psychotic symptoms following the index admission found that in 114 patients (60.3%) the psychotic symptoms resolved in less than 1 month, in 56 (29.6%) the psychotic symptoms persisted for 1 to 6 months, and in 19 (10.1%) the psychotic symptoms persisted for longer than 6 months.

Comparison of the characteristics of the three groups of patients at the time of the index admission identified several significant differences (Table 2). Patients with psychotic symptoms that persisted more than 6 months after stopping illicit drug use were more likely than patients in the other two groups to have a family history of mental illness, and to have an earlier age of onset and a longer duration of drug abuse prior to the index admission. Compared to patients with 1 to 6 months of psychotic symptoms following termination of illicit drug use, those with less than one month of psychotic symptoms were less likely to have a positive family history of mental illness, had a shorter duration of drug use and were less likely to use multiple drugs of abuse at the time of the index admission.

Comparison of the characteristics of the three groups of patients at the time of the follow-up also identified significant differences. Patients with psychotic symptoms that persisted more than 6 months after stopping illicit drug use were more likely than patients in the other two groups to have been rehospitalized during the follow-up period and to have psychotic symptoms at the time of follow-up. Compared to patients with 1 to 6 months
of psychotic symptoms following termination of illicit drug use, those with less than one month of psychotic symptoms were less likely to be rehospitalized over the follow-up period and had fewer positive and negative symptoms at the time of follow-up.

After excluding the patients who had used illicit drugs in the six months prior to the follow-up, most of the 16 patients whose symptoms persisted for more than 6 months after stopping illicit drug use still had clinically significant psychotic symptoms at the time of follow-up (that is, long after stopping illicit drug use); in 8 of these patients (4.2% of all patients followed-up) the diagnosis had changed to schizophrenia. None of the patients in the other two groups who had not used illicit drugs in the prior six months had clinically significant psychotic symptoms at the time of follow-up. Persistent psychotic symptoms were more common in those with a positive family history of mental illness, an earlier age of onset of illicit drug use and a longer history of illicit drug use. Almost 90% of the patients restarted illicit drug use at some point after treatment for their psychosis symptoms.

The relative role of predisposing factors and neurotoxic factors in the induction of chronic psychosis among individuals who use illicit drugs remains controversial. Earlier studies in the United States had suggested that most patients who converted to a chronic psychosis following illicit drug use had a predisposition to psychotic illness, but more recent studies from Japan and Thailand — which have experienced an epidemic of methamphetamine abuse in recent decades — suggest that chronic methamphetamine abuse in recent decades suggest that chronic methamphetamine abuse can induce chronic psychotic states independent of other predisposing factors. For example, the study by Kittirattananapiboon and colleagues followed 449 patients several years after a first admission for psychotic symptoms associated with methamphetamine abuse and found that over the follow-up period 39% required rehospitalization and 38% had their diagnosis changed to schizophrenia because

### Table 1. Characteristics at time of index admission of patients with psychotic symptoms induced by illicit drug use admitted to Kangning Hospital, Shenzhen, 2003-2010

|                          | All Patients (n=258) | Patients with single drug of abuse (n=77) | Patients with multiple drugs of abuse (n=181) | statistic | p     |
|--------------------------|----------------------|-----------------------------------------|---------------------------------------------|-----------|-------|
| Male (n, %)              |                      |                                         |                                             |           |       |
| 218 (84.5%)              | 66 (85.7%)           | 152 (84.0%)                             | X²=0.09                                     | 0.817     |       |
| Age in years (mean, sd)  | 28.7 (9.6)           | 24.5 (8.3)                              | 29.7 (9.2)                                 | t=6.07    | 0.019 |
| Duration of education in years (mean, sd) | 7.4 (5.7) | 7.9 (4.6) | 6.8 (5.0) | t=0.37 | 0.561 |
| Unemployed (n, %)        |                      |                                         |                                             |           |       |
| 202 (78.3%)              | 60 (79.9%)           | 142 (78.5%)                             | X²=0.02                                     | 0.906     |       |
| Family history of psychiatric illness (n, %) | 26 (10.1%) | 7 (9.1%) | 19 (10.5%) | X²=0.93 | 0.230 |
| Age of first taking illicit drugs (mean, sd) | 22.4 (9.2) | 21.8 (8.1) | 22.7 (5.5) | t=0.06 | 0.894 |
| Duration of drug use in years (mean, sd) | 6.9 (5.8) | 5.4 (4.3) | 7.6 (5.2) | t=3.82 | 0.037 |

Main drug used in month prior to admission (n, %)
|                | All Patients (n=258) | Patients with single drug of abuse (n=77) | Patients with multiple drugs of abuse (n=181) | statistic | p     |
|----------------|----------------------|-----------------------------------------|---------------------------------------------|-----------|-------|
| Heroin        |                      |                                         |                                             |           |       |
| 40 (15.5%)    | 9 (11.7%)            | 31 (17.1%)                              | X²=1.29                                     | 0.732     |       |
| Methamphetamine | 122 (47.3%) | 38 (49.4%) | 84 (46.4%) |           |       |
| Ecstasy       | 59 (22.9%)           | 19 (24.7%)                              | 40 (22.1%)                                 |           |       |
| Ketamine      | 37 (14.3%)           | 11 (14.3%)                              | 26 (14.4%)                                 |           |       |
| Positive symptom score at admission (mean, sd) | 25.6 (10.4) | 24.1 (8.1) | 26.2 (9.8) | t=0.13 | 0.714 |
| Negative symptom score admission (mean, sd) | 13.1 (6.0) | 11.5 (4.6) | 13.8 (5.5) | t=0.39 | 0.527 |
| Duration of index admission in days (mean, sd) | 23.45 (10.8) | 22.71 (9.6) | 23.76 (10.1) | t=0.29 | 0.623 |

As retrospectively assessed using 7 items from the Positive and Negative Syndrome Scale (range in score: 7-49)
Table 2. Comparison of characteristics of patients with psychotic symptoms induced by illicit drug use whose psychotic symptoms after the index admission persisted for different durations after stopping the use of illicit drugs

| Characteristics at time of index admission | All patients (n=189) | [A] <1 month (n=114) | [B] 1-6 months (n=56) | [C] >6 months (n=19) | statistic | p | multiple comparisons a |
|-------------------------------------------|---------------------|----------------------|----------------------|----------------------|----------|---|----------------------|
| Male [n, %]                               | 155 (82.0%)         | 93 (81.6%)           | 46 (82.1%)           | 16 (84.2%)           | X²=0.04  | 0.896 ns |                      |
| Age in years (mean, sd)                   | 27.9 (8.9)          | 28.3 (8.1)           | 27.4 (7.9)           | 27.1 (7.5)           | F=0.03   | 0.934 ns |                      |
| Duration of education in years (mean , sd) | 8.1 (4.0)           | 8.3 (4.2)            | 7.5 (3.6)            | 8.8 (4.5)            | F=0.05   | 0.879 ns |                      |
| Unemployed [n, %]                         | 146 (77.3%)         | 90 (79.0%)           | 42 (75.0%)           | 14 (73.7%)           | X²=0.09  | 0.821 ns |                      |
| Family history of psychiatric illness [n, %] | 19 (10.1%)         | 8 (7.0%)             | 7 (12.5%)            | 4 (21.1%)            | X²=77.54 | <0.001 A<B<C         |
| Age of first taking illicit drugs (mean, sd) | 22.5 (7.5)        | 24.3 (4.9)           | 22.4 (5.3)           | 18.0 (4.8)           | F=9.77   | 0.024 C<B,A         |
| Duration of drug use in years (mean, sd)  | 5.4 (4.7)           | 4.1 (3.4)            | 6.9 (3.3)            | 8.5 (4.2)            | F=29.15  | <0.001 A<B<C         |

| Characteristics at time of follow-up |
|--------------------------------------|
| Duration of follow-up period in months (mean, sd) | 49.7 (18.1) | 49.1 (16.3) | 51.6 (15.2) | 48.7 (15.7) | F=0.00 | 0.950 ns |                      |

| Characteristics of patients with no illicit drug use in last 6 months d |
|-----------------------------------------------|
| Positive symptom score (mean, sd) d           | 8.1 (2.9)    | 7.1 (0.4)    | 7.4 (0.7)    | 15.5 (4.5)    | F=223.95  | <0.001 A,B,C         |

| Persons with no illicit drug use in last 6 months d |
|-----------------------------------------------|
| Positive symptom score (mean, sd) d           | 7.8 (2.1)    | 7.1 (0.3)    | 7.2 (0.6)    | 12.3 (4.0)    | F=106.60  | <0.001 A,B,C         |

| Any positive or negative symptom [n, %] c     |
|-----------------------------------------------|
| Persons with no illicit drug use in last 6 months d | 73 (38.6%) | 29 (23.4%) | 25 (44.6%) | 18 (94.7%) | X²=247.87 | <0.001 A<B<C         |

a Multiple comparison of categorical variables were made using a Tukey-type multiple comparison method based on an arcsin transformation of the original proportions. b As retrospectively assessed using 7 items from the Positive and Negative Syndrome Scale (range in score: 7-49). c Any of the 14 items from the PANSS coded as 2 (very mild) or more. d The number of cases used in this analysis are as follows: 157 cases in total, 95 cases <1 month, 46 cases 1-6 months, 16 cases >6 months.

the psychotic symptoms persisted in the absence of continued drug abuse. Our study finds a much lower rehospitalization rate (13%) and a much lower rate of conversion to schizophrenia (4%). Moreover, we did not find that methamphetamine abuse is more likely to result in persistent psychosis than other types of illicit drugs. However, these differences across studies could be due to cross-national differences in the severity of drug abuse or due to differences in the algorithms used to apply the diagnosis of schizophrenia to individuals with a chronic history of illicit drug use.

A previous report by Liu and colleagues [14] found...
that 5.4% of community members in mainland China had a positive family history for mental illness. This is comparable to the 7% rate of a positive family history of mental illness we found in subjects whose psychotic symptoms resolved within one month of stopping illicit drugs but is much lower than the 21% rate we found in those whose psychotic symptoms persisted for 6 months or longer after stopping the illicit drugs. A study by Chen and colleagues[15] reported that individuals who used methamphetamines were more likely to have psychotic symptoms and to have psychotic symptoms that persisted longer if there was a family history of schizophrenia. Taken together these findings support the hypothesis that chronic psychosis is a more likely outcome of illicit drug use in individuals with a genetic predisposition for psychosis.

Our results also support the neurotoxic hypothesis. Previous studies[16,17] suggest that longer use of illicit drug is associated with greater damage to the structure and functioning of the central nervous system and, thus, more likely to result in chronic psychosis. Our finding that an earlier age of onset of illicit drug use (when the brain is more susceptible to damage) and longer use of illicit drugs were associated with persistent psychosis following termination of illicit drug use supports this hypothesis.

4.2 Limitations

The major limitation to the study is that several variables depended on retrospective reports of the patients and their family members. In most cases psychotic symptoms resolved prior to discharge from the index hospitalization, so determination of the persistence of psychotic symptoms after stopping illicit drug use was reasonably reliable; but in the minority of patients who continued to have psychotic symptoms at the time of the index discharge we had to depend on the retrospective reports of the patients and their family members. The information about restarting illicit drug use also depended on retrospective reports, but almost 90% of the subjects indicated that they had relapses of illicit drug use, so underreporting is not likely a serious problem.

Our classification of the persistence of psychotic symptoms depended on the persistence of symptoms at the time of the first psychiatric hospitalization. It is certainly possible that some patients had a rapid recovery of psychotic symptoms after the first episode but had a more delayed recovery of psychotic symptoms following subsequent episodes of illicit drug use. This possible misclassification of patients is more likely to have occurred in the 13% of subjects who had rehospitalizations following the index discharge.

The huge variability in the follow-up period (from 13 months to 108 months) could have skewed the reported rates of rehospitalization and reintiation of drug use during the follow-up period, but there were no significant differences in follow-up times between the three groups of subjects so this problem probably did not affect comparisons across the groups.

Other factors that could affect the interpretation of our results include the following. These patients were hospitalized for treatment of their psychiatric symptoms at one psychiatric hospital in China so it is not possible to say how representative they are of all illicit drug users with psychotic symptoms in China (many of whom go untreated or are treated in drug rehabilitation programs) or of all illicit drug users who are treated in Chinese psychiatric hospitals. We did not have a large enough sample to stratify the analysis by type of illicit drug or to conduct a multivariate analysis that could help to distinguish the relative contribution of genetic and neurotoxic factors. We assessed the duration of drug use but did not assess the severity of use (dose, method of administration, etc). Finally, no standardized diagnostic algorithm was applied to determine whether or not a patient’s diagnoses should change to schizophrenia; this determination was based on the judgment of the treating clinician.

4.3 Significance

The proportion of patients with persistent psychotic symptoms following illicit drug use, though lower than reported in other countries, is nevertheless a serious public health problem in China. Some of these individuals progress to schizophrenia, a chronic condition that has very serious, lifelong effects on the individual, the family and the community. Further prospective studies are needed to determine the relative roles of the neurotoxic effects of illicit drugs and the predisposing characteristics of individuals who use illicit drugs, but it is most probable that both factors are important in the development of chronic psychosis in these individuals. The very high rates of recidivism in this sample suggest that the best option for reducing illicit drug-induced chronic psychoses is to develop, test and promulgate innovative approaches to prevent the onset and to decrease the duration of illicit drug use.

Conflict of interest

The authors report no conflict of interest related to this study.

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精神活性物质所致精神病性障碍的转归调查

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摘要

背景  国内关于精神活性物质所致精神病性障碍的长期预后尚不清楚。
目的  对因吸毒出现精神症状而曾住院治疗的患者，评估其精神症状的严重程度和病程。
方法  于2012年对2003年至2010年期间首次在深圳市康宁医院住院、入院前1个月内曾非法使用过毒品、被诊断为精神活性物质所致精神病性障碍的患者进行随访，随访期为13~108个月。通过对患者及其同住的家庭成员的调查，了解患者出院后复吸情况及精神病性症状演变情况。
结果  受调查的258例患者主要特点为年轻、男性、无业，主要使用的毒品为冰毒，入院时使用毒品的平均时间为7年。共189例完成随访，其中168例（89%）复吸，25例（13%）在随访期间再次住院。114例（60%）患者的精神症状在停吸1个月内缓解，25例（30%）的精神症状持续1~6个月，19例（10%）的精神症状持续存在超过6个月（其中8例的诊断改为精神分裂症）。与症状持续时间较短的其他两组相比，症状持续6个月以上这组存在精神疾病家族史的比例最高，开始吸毒的年龄最小，首次住院前毒品使用时间最长，随访期间再住院的比例最高，随访时存在精神症状的比例也最高。
结论  多数精神活性物质所致精神病性障碍患者预后较好，但首次吸毒年龄小，吸毒年限长，存在精神疾病家族史者容易发展为慢性精神病。需要进一步开展前瞻性研究，以明确毒品的神经毒性作用与个体素质之间的相互关系在吸毒者出现慢性精神病中所起的作用。