Original Article

# Clinical Characteristics and Rehospitalization in Patients with Schizophrenia with or without History of Amphetamine Abuse

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## Abstract

**Objective:** In this study, we intended to study the differences of the clinical characteristics between patients with schizophrenia with or without history of amphetamine abuse and risk factors of rehospitalization. **Methods:** We used medical records and reviewed electronic database to collect the two schizophrenia groups discharged from the Taoyuan Psychiatric Center from January 1, 2012, to December 31, 2015. Patients with and without amphetamine abuse were defined as case group and control group, respectively. The patients' demographic data and clinical variables were extracted and examined. **Results:** We identified 80 patients in the case group and 142 patients in the control group. Up to 32.5% of the case group patients still showed a positive urine amphetamine test. The univariate analysis showed that significant differences existed in gender ($p < 0.001$), age ($p < 0.001$), marriage ($p < 0.05$), education ($p < 0.001$), psychiatric comorbidity ($p < 0.05$), family history of schizophrenia ($p < 0.01$), family history of illicit substance use ($p < 0.001$), history of suicide ($p < 0.01$), history of violence ($p < 0.001$), hospitalization days ($p < 0.001$), and rehospitalization rate ($p < 0.05$). The result of the logistic regression showed that the number of previous admissions was a positive predictor of rehospitalization and that with family history of schizophrenia was a negative predictor of rehospitalization. The Cox proportional hazards regression model analysis showed that the number of previous admissions was still a positive predictive factor for the rehospitalization. **Conclusion:** In this study, the characteristics of two study patient groups were different. Patients with schizophrenia and with a history of amphetamine abuse had a tendency of amphetamine abuse and a higher rate of rehospitalization. Further treatment for amphetamine abstinence in the community for this population is warranted to strengthen the study results.

**Key words: amphetamine-induced psychosis, amphetamine/abuse, re-admission, schizophrenia**
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## Introduction

Although the worldwide drug abuse trends have been changed over the decades, amphetamine abuse reached its peak popularity in the 1990s and still continues to be popular in the United States of America and Asian countries including Taiwan [1-4]. Amphetamine was reported as the most widely used illicit drug in Taiwan from 1999 to 2011 [4]. Amphetamine is a highly addictive central nervous system stimulant. Amphetamine abuse is associated with a wide range of health harms, such as psychosis and other mental disorders, cardiovascular and renal dysfunction, infectious diseases, and even death.

The neurotoxicity of amphetamines can cause psychosis in amphetamine users has been documented since the 1950s [5]. Because of its close clinical similarity to acute paranoid schizophrenia, amphetamine-induced psychosis was even used as a useful experimental model for schizophrenia in both basic and clinical studies [6]. Amount and duration of use, age at the first time of use, familial vulnerability, and personality factors are the determinants for the development of psychosis [7]. Many studies also exist comparing the similarities and differences between amphetamine-induced psychosis and schizophrenia [7-10]. They showed that amphetamine-induced psychosis has similar positive symptomatology, but less

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negative and cognitive symptoms, and that the overall episode of amphetamine-induced psychosis is resolved faster and more completely than that of schizophrenia [7-10].

Besides, after the chronicity of psychotic symptoms and repeated relapse of episodes, those episodes are often re-diagnosed by clinicians as "schizophrenia" according to the universal diagnostic system (*the Diagnostic and Statistical Manual* [*DSM*] or *the International Classification of Diseases* [*ICD*]) [11]. Many studies have focused on the occurrence of this conversion, and the overall cumulative risk for conversion to schizophrenia is about 11.3%–32.2% [12]. Previous studies showed that the risk factors of conversion include young age at diagnosis of substance-induced psychotic disorder, male gender, self-harm behavior, longer duration of first admission, and comorbid alcohol use disorder [13, 14]. The majority of conversions to a schizophrenia spectrum diagnosis occur during the first three years of the diagnosis of substance-induced psychotic disorder [15].

The psychosocial and behavioral problems in the clinical course of these schizophrenia patients with history of amphetamine abuse are different from the native schizophrenia patients who have no history of amphetamine abuse, but only limited relevant research exists in the literature [16]. In this study, we intended to study the differences of demographic and clinical characteristics between those two groups of patients and to find out the predictive factors that affected rehospitalization after a one-year acute psychiatric ward discharge.

## Methods

### Study setting

This study was conducted at the Taoyuan Psychiatric Center (TYPC), a major public psychiatric hospital in Taiwan. TYPC provides 282 acute psychiatric beds and 380 chronic psychiatric beds, which accounts for about 50% of the total acute psychiatric beds in Taoyuan City, which is a municipality with a population of 2.1 million people.

### Study participants

We used medical records and reviewed electronic database to collect information of patients with schizophrenia discharged from the TYPC acute ward during the past four years (January 1, 2012 to December 31, 2015). The age was between 20 and 65 years. We included eligible patients who had main diagnosis with the *ICD*, *Ninth Revision, Clinical Modification* code of 295.xx and schizoaffective disorder. We excluded those who were: (a) comorbid with mental retardation or organic brain disease; (b) being discharged to a general hospital because of medical disease or surgical emergence condition; and (c) being transferred to a chronic ward, day-care unit, half-way house, or nursing home.

The case group was identified as the patients with schizophrenia and with a history of amphetamine abuse or positive urine amphetamine test or ever diagnosed as amphetamine-induced psychotic disorder previously. The control group was chosen as the patients with schizophrenia who were admitted on the same day or consecutive day as the case group but without a history of amphetamine abuse. The medical charts of the two patient groups were reviewed to collect their demographic data (gender, age, age of onset, age of first hospital visit, marital status, living status, education level, and employment state) and clinical information (course of schizophrenia, psychiatric comorbidity, physical comorbidity, smoking, alcohol misuse, prescription drug misuse, amphetamine or other illicit substance abuse, result of amphetamine urine test, history of suicide or violence, family history of schizophrenia, family history of illicit substance abuse, route for hospitalization, admission status, days of hospital stay, self-harm or violence in the hospital, restraint in the hospital, discharge disposition, number of previous hospitalization, rehospitalization, time to rehospitalization, ratio of prescribed daily dose versus defined daily dose of antipsychotics, and concomitant medication with mood stabilizers) of the index admission.

A study assistant with a more than a five-year experience in psychiatric research extracted the data. The first author (WCH), a board-certificated psychiatrist, supervised and discussed on the medical records and extraction results regularly. This study was approved by the institutional review board of TYPC (IRB number = B20171102 and date of approved = September 12, 2017) without the need of obtaining written informed consents from the study participants.

### Statistical analysis

In this study, we used Chi-square test to compare categorical variables and independent *t*-test to compare continuous variables. Unconditional logistic regression and Cox regression model were used to explore the probable risk factors of rehospitalization and calculate the odds ratios or hazard ratios. We included covariates in the multivariate logistic regression model or Cox regression model if we deemed them to be of clinical significance, such as age, gender, and illicit substance use, or if they had a univariate, $p < 0.05$. We did the Homer–Lemeshow goodness-of-fit test to assess adequacy of the multivariate models of logistic regression.

The differences between the groups were considered significant if $p < 0.05$ (two tails). All study data were analyzed using Statistical Package for the Social Science version 20 (SPSS Inc., Chicago, Illinois, USA).

## Results

We identified 222 patients with schizophrenia from January 1, 2012 to December 31, 2015, with 80 patients in the case group and 142 patients in the control group. Table 1 presents the demographic and clinical data of the whole study population. The mean age was 39.1 ± 10.6 years, and 56.8% were male. Of the whole sample, 105 (47.3%) cases were rehospitalized within the following year after the index hospitalization. The mean time to rehospitalization was 242.2 ± 147.1 days.

**Table 1.** Demographic and clinical characteristics of the whole study population ($n$ = 222)

| Variable | $n$ (%) |
|---|---|
| Gender | |
| Male | 126 (56.8) |
| Female | 96 (43.2) |
| Age (years), mean ± SD | 39.1 ± 10.6 |
| Age of onset (years), mean ± SD | 24.5 ± 9.2 |
| Age of the first hospital visit (years), mean ± SD | 29.1 ± 10.6 |
| Marital status | |
| Married | 40 (18.0) |
| Single/divorced/widowed | 182 (82.0) |
| Living state | |
| Live with friends or family | 184 (82.9) |
| Living alone/live in institutions | 38 (17.1) |
| Education level | |
| Elementary school/middle school | 85 (38.3) |
| High school/college/graduate school | 137 (61.7) |
| Employment | |
| No | 195 (87.8) |
| Yes | 27 (12.2) |
| Psychiatric comorbidity (ICD-9: 290.xx - 319 excluded 303.xx, 304.xx, 305.xx) | |
| No | 174 (78.4) |
| Yes | 48 (21.6) |
| Physical comorbidity | |
| No | 108 (48.6) |
| Yes | 114 (51.4) |
| Smoking | |
| No | 101 (45.5) |
| Yes | 121 (54.5) |
| Alcohol misuse | |
| No | 142 (64.0) |
| Yes | 80 (36.0) |
| Prescription drug misuse | |
| No | 219 (98.6) |
| Yes | 3 (1.4) |
| Illicit substance abuse | |
| No | 142 (64.0) |
| Yes | 80 (36.0) |
| Amphetamine abuse | |
| No | 142 (64.0) |
| Yes | 80 (36.0) |
| Amphetamine urine test | |
| Negative/un-test | 196 (88.3) |
| Positive | 26 (11.7) |
| Family history of schizophrenia | |
| No | 176 (79.3) |
| Yes | 46 (20.7) |
| Family history of illicit substance abuse | |
| No | 205 (92.3) |
| Yes | 17 (7.7) |
| History of suicidal attempt | |
| No | 182 (82.0) |
| Yes | 40 (18.0) |
| History of violence | |
| No | 117 (52.7) |
| Yes | 105 (47.3) |

*Contd...*

**Table 1.** Contd...

| Variable | *n* (%) |
|---|---|
| Route for hospitalization | |
| Through out-patient clinic | 52 (23.4) |
| Through emergency department | 170 (76.6) |
| Compulsory hospitalization | |
| No | 215 (96.8) |
| Yes | 7 (3.2) |
| Previous admissions (frequency), mean ± SD | 3.7 ± 4.2 |
| Hospitalization days (day), mean ± SD | 58.0 ± 40.2 |
| Self-harm in hospital | |
| No | 219 (98.6) |
| Yes | 3 (1.4) |
| Violence in hospital | |
| No | 205 (92.3) |
| Yes | 17 (7.7) |
| Restraint in hospital | |
| No | 140 (63.1) |
| Yes | 82 (36.9) |
| Concomitant mood stabilizers | |
| No | 170 (76.6) |
| Yes | 52 (23.4) |
| Discharge disposition | |
| Going home | 203 (91.4) |
| Going to half-way house/institutions | 19 (8.6) |
| Rehospitalization | |
| No | 117 (52.7) |
| Yes | 105 (47.3) |
| Time to rehospitalization (days), mean ± SD | 242.2 ± 147.1 |
| PDD/DDD ratio (oral antipsychotics), mean ± SD | 1.3 ± 0.9 |

SD, standard deviation; PDD, prescribed daily dose; DDD, defined daily dose

Table 2 shows the comparison of the demographic and clinical data between the two study groups. In the univariate analysis, the case group had a significantly higher male ratio (73.8% vs. 47.2%, $p < 0.001$), younger age (36.1 ± 7.5 years vs. 40.8 ± 11.6 years, $p < 0.001$), younger age of the first hospital visit (27.4 ± 7.6 years vs. 30.0 ± 11.8 years, $p < 0.05$), less married (10.0% vs. 22.5%, $p < 0.05$), lower education level (41.2% vs.73.2%, $p < 0.001$), more psychiatric comorbidity (88.7% vs. 34.5%, $p < 0.001$), more smoking (91.2% vs. 33.8%, $p < 0.001$), more alcohol misuse (62.5% vs. 21.1%, $p < 0.001$), less family history of schizophrenia (10.0% vs. 26.8%, $p < 0.01$), more family history of illicit substance use (18.7% vs. 1.4%, $p < 0.001$), more history of suicide (27.5% vs. 12.7%, $p < 0.01$), more history of violence (63.7% vs. 38.0%, $p < 0.001$), less hospitalization days (44.5 ± 25.6 days vs. 65.6 ± 44.7 days, $p < 0.001$), and a higher rate of rehospitalization (56.2% vs. 42.3%, $p < 0.05$).

Table 3 displays the results of the risk factors for rehospitalization in the logistic regression model and Cox proportional hazards regression model. We found that family history of schizophrenia (adjusted odds ratio = 0.401, 95% confidence interval [CI] = 0.182–0.884, $p < 0.05$) and number of previous admissions (aOR = 1.342, 95% CI = 1.076–1.674, $p < 0.01$) were significantly associated with increased risk of one-year rehospitalization in the logistic regression model. The model fitted appropriately (Hosmer–Lemeshow statistics = 5.69; $p = 0.472$). In the Cox proportional hazards regression model, we found that previous admission was the only one factor significantly associated with rehospitalization (adjusted hazard ratio = 1.108, 95% CI = 1.064–1.154, $p < 0.05$).

## Discussion

To our knowledge, this study is one of the first studies to focus on the subgroup of schizophrenia who is converted from amphetamine-induced psychotic disorder with history of amphetamine abuse. It is pivotal to reveal the clinical aspects of those patients after the conversion of the disease. This study also provides important information related to clinical psychiatry, public health, and drug control about this subpopulation.

In our study (Table 2), schizophrenia with history of amphetamine abuse had significantly higher rehospitalization rate ($p < 0.05$), and more than 30% (32.5%) of those patients still showed a positive urine amphetamine test in the index hospitalization. The positive rate of our report is higher compared to that in the previous study (22%) [17]. This finding maybe due to our admission case selection was focusing on specific schizophrenia rather than general psychiatric

**Table 2.** Univariate comparisons between case group and control group

| Variable | Case group ($n$ = 80), $n$ (%) | Control group ($n$ = 142), $n$ (%) |
|---|---|---|
| Gender*** | | |
| Male | 59 (73.8) | 67 (47.2) |
| Female | 21 (26.2) | 75 (52.8) |
| Age (years), mean ± SD*** | 36.1 ± 7.5 | 40.8 ± 11.6 |
| Age of onset (years), mean ± SD*** | 23.5 ± 7.6 | 25.0 ± 10.1 |
| Age of the first hospital visit, mean ± SD* | 27.4 ± 7.6 | 30.0 ± 11.8 |
| Marital status* | | |
| Married | 8 (10.0) | 32 (22.5) |
| Single/divorced/widowed | 72 (90.0) | 110 (77.5) |
| Living state | | |
| Live with friends or family | 70 (87.5) | 114 (80.3) |
| Living alone/living in institutions | 10 (12.5) | 28 (19.7) |
| Education level*** | | |
| Elementary school/middle school | 47 (58.8) | 38 (26.8) |
| High school/college/graduate school | 33 (41.2) | 104 (73.2) |
| Employment | | |
| No | 66 (82.5) | 129 (90.8) |
| Yes | 14 (17.5) | 13 (9.2) |
| Psychiatric comorbidity (ICD-9: 290.XX-319 exclude 303.xx, 304.xx, 305.xx)* | | |
| No | 69 (86.2) | 105 (73.9) |
| Yes | 11 (13.8) | 37 (26.1) |
| Physical comorbidity | | |
| No | 39 (48.8) | 69 (48.6) |
| Yes | 41 (51.2) | 73 (51.4) |
| Smoking*** | | |
| No | 7 (8.8) | 94 (66.2) |
| Yes | 73 (91.2) | 48 (33.8) |
| Alcohol misuse*** | | |
| No | 30 (37.5) | 112 (78.9) |
| Yes | 50 (62.5) | 30 (21.1) |
| Prescription drug misuse | | |
| No | 78 (97.5) | 141 (99.3) |
| Yes | 2 (2.5) | 1 (0.7) |
| Amphetamine urine test*** | | |
| Negative/un-test | 54 (67.5) | 142 (100.0) |
| Positive | 26 (32.5) | 0 (0.0) |
| Family history of schizophrenia** | | |
| No | 72 (90.0) | 104 (73.2) |
| Yes | 8 (10.0) | 38 (26.8) |
| Family history of illicit substance abuse*** | | |
| No | 65 (81.3) | 140 (98.6) |
| Yes | 15 (18.7) | 2 (1.4) |
| History of suicidal attempt** | | |
| No | 58 (72.5) | 124 (87.3) |
| Yes | 22 (27.5) | 18 (12.7) |
| History of violence*** | | |
| No | 29 (36.3) | 88 (62.0) |
| Yes | 51 (63.7) | 54 (38.0) |
| Route for hospitalization | | |
| Through outpatient clinic | 14 (17.5) | 38 (26.8) |
| Through emergency department | 66 (82.5) | 104 (73.2) |
| Compulsory hospitalization | | |
| No | 79 (98.8) | 136 (95.8) |
| Yes | 1 (1.2) | 6 (4.2) |

*Contd...*

**Table 2.** Contd...

| Variable | Case group ($n$ = 80), $n$ (%) | Control group ($n$ = 142), $n$ (%) |
|---|---|---|
| Previous admissions (frequency), mean ± SD | 3.9 ± 3.4 | 3.6 ± 4.6 |
| Hospitalization days (day), mean ± SD*** | 44.5 ± 25.6 | 65.6 ± 44.7 |
| Self-harm in hospital | | |
| No | 79 (98.8) | 140 (98.6) |
| Yes | 1 (1.2) | 2 (1.4) |
| Violence in hospital | | |
| No | 75 (93.8) | 130 (91.5) |
| Yes | 5 (6.2) | 12 (8.5) |
| Restraint in hospital | | |
| No | 53 (66.3) | 87 (61.3) |
| Yes | 27 (33.7) | 55 (38.7) |
| Medication combined with mood stabilizers | | |
| No | 64 (80.0) | 106 (74.6) |
| Yes | 16 (20.0) | 36 (25.4) |
| Discharge disposition | | |
| Going home | 77 (96.3) | 126 (88.7) |
| Going to half-way house/institutions | 3 (3.7) | 16 (11.3) |
| Rehospitalization* | | |
| No | 35 (43.8) | 82 (57.7) |
| Yes | 45 (56.2) | 60 (42.3) |
| Time to rehospitalization days, mean ± SD | 220.0 ± 147.1 | 254.7 ± 146.2 |
| PDD/DDD (oral antipsychotics), mean ± SD | 1.2 ± 1.1 | 1.3 ± 0.8 |

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, using Chi-square test or $t$-test when appropriate ($n$ = 222).
SD, standard deviation; PDD, prescribed daily dose; DDD, defined daily dose

inpatient. We suggest that these patients cannot abstain from amphetamine use in their community living and that amphetamine abuse is still an important factor for causing symptoms recurrence and rehospitalization. Therefore, we advocate that they should be treated with special treatment programs on amphetamine abuse in the community after their being discharged.

In our study (Table 2), significant differences existed between case group and control group in gender ratio ($p < 0.001$), age of first-time doctor visit ($p < 0.05$), hospitalization age ($p < 0.001$), marital status ($p < 0.05$), education level ($p < 0.001$), psychiatric comorbidity ($p < 0.001$), tobacco/alcohol use ($p < 0.001$), family history of illicit drug use ($p < 0.001$), suicide history ($p < 0.01$), violence history ($p < 0.001$), days of hospital stay ($p < 0.001$), rehospitalization rate ($p < 0.05$), and family heredity ($p < 0.01$) in the univariable comparisons. Those two study groups show significant differences in several variables; it is consistent with the study hypothesis that the two groups of patients may be different in basic characteristics. The case group showed significantly higher male ratio ($p < 0.001$), younger age ($p < 0.001$), less married ($p < 0.05$), lower education achievement ($p < 0.001$), more psychiatric comorbidity ($p < 0.001$), more tobacco/alcohol use ($p < 0.001$), more history of suicidal attempt ($p < 0.01$), more history of violence ($p < 0.001$), less hospitalization days ($p < 0.001$), higher rehospitalization rate ($p < 0.05$), less family history of schizophrenia ($p < 0.01$), and more family history of illicit substance use ($p < 0.001$). We find that the demographic characteristics (including gender, age, education, and marriage) of the patients with schizophrenia and with history of amphetamine abuse remain similar to the amphetamine abusers reported in a past study [18]. Therefore, we can also challenge differences between the diagnostic criteria of *DSM-5* and *ICD-10* and suggest that it is more appropriate to recognize them as persistent or chronic amphetamine-induced psychotic disorder rather than ordinary schizophrenia.

In this study (Table 2), the other variables (including age of onset, living status, employment, physical comorbidity, prescription drug misuse, patient visits, compulsory hospitalization, self-injury/violence in hospital, restraint implementation, discharge disposition, time to rehospitalization, and the daily dose of antipsychotic drugs) did not show significant differences between those two groups. The results might reflect on the clinical facts that the two groups of patients who have been ill for > 10 years after the onset of psychosis, no differences exist in the treatment modalities. This may also imply the hospitalization care under Taiwan's National Health Insurance does not provide different treatment interventions.

The logistic regression model analysis (Table 3) showed that the number of previous admissions was a positive predictor of rehospitalization within one year after discharge and that the family history of schizophrenia was a negative predictor of rehospitalization within one year after discharge. The Cox proportional hazards regression model analysis

**Table 3.** Factors associated with rehospitalization in the logistic regression model and Cox regression model

| Logistic regression model | |
|---|---|
| Variable | aOR (95% CI) |
| Family history of schizophrenia* | 0.401 (0.182 - 0.884) |
| Previous admissions*** | 1.240 (1.123 - 1.370) |
| **Cox regression model** | |
| Variable | Adjusted hazard ratio (95% CI) |
| Previous admissions*** | 1.108 (1.064 - 1.154) |

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
CI, confidence interval; aOR, adjusted odds ratio

(Table 3) also showed that the number of previous admissions was also a positive predictive factor for the rehospitalization. Our results of this study are compatible to the past reports such as hospitalization in the preceding year is a predictor of rehospitalization in schizophrenia and previous admissions increased the likelihood of rehospitalization for the patient with substance use disorder [19, 20]. Besides, it is also reasonable that patients with family history of schizophrenia may decrease the risk of future rehospitalization compared with the patients with schizophrenia but without family history. Patients with family history of schizophrenia in this study imply that they are the group without amphetamine or other illicit use and subsequently decrease the risk of rehospitalization.

### *Study limitations*

The readers are warned against over-extrapolating the study results because it has four major limitations:

- This study is retrospective in nature.
- The case sample was composed of patients who were discharged from the acute ward rather than home or somewhere outside of the hospital. This approach would lose those cases transferred to the chronic ward, day-care ward, and other institutes. Furthermore, we also excluded patients who were transferred to the general hospital due to medical and surgical complications. Therefore, the overall representativeness of the study sample could have been compromised.
- Our data of rehospitalization were only tracked over a period of one year, and we cannot estimate the effects in the long-term period. We recommend that future study can extend the tracking period more than one-year to obtain long-term data.
- We included the data of patients of only from one single psychiatric center. The findings from this study may not be generalized to other studies because of differences in local practice patterns.

### *Summary*

The differences of demographic and clinical data supported the hypothesis that the schizophrenia patients with history of amphetamine abuse are different from the ordinary schizophrenia patient who has no history of amphetamine abuse. The schizophrenia patients with history of amphetamine abuse often still have amphetamine intake and have a higher risk of rehospitalization. We recommend that treatment for abstinence from amphetamine use in the community should be particularly enforced after their discharge to reduce the chance of future hospitalization in this population.

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## Conflicts of Interest

The authors declare no conflicts of interest for writing this paper.

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