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The risk and associated factors of methamphetamine psychosis in methamphetamine-dependent patients in Malaysia

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Abstract

Objective: The objective of this study was to determine the risk of lifetime and current methamphetamine-induced psychosis in patients with methamphetamine dependence. The association between psychiatric co-morbidity and methamphetamine-induced psychosis was also studied.

Methods: This was a cross-sectional study conducted concurrently at a teaching hospital and a drug rehabilitation center in Malaysia. Patients with the diagnosis of methamphetamine based on DSM-IV were interviewed using the Mini International Neuropsychiatric Interview (M.I.N.I.) for methamphetamine-induced psychosis and other Axis I psychiatric disorders. The information on sociodemographic background and drug use history was obtained from interview or medical records.

Results: Of 292 subjects, 47.9% of the subjects had a past history of psychotic symptoms and 13.0% of the patients were having current psychotic symptoms. Co-morbid major depressive disorder (OR = 7.18, 95 CI = 2.612–19.708), bipolar disorder (OR = 13.807, 95 CI = 5.194–36.706), antisocial personality disorder (OR = 12.619, 95 CI = 6.702–23.759) and heavy methamphetamine uses were significantly associated with lifetime methamphetamine-induced psychosis after adjusted for other factors. Major depressive disorder (OR = 2.870, CI = 1.154–7.142) and antisocial personality disorder (OR = 3.299, 95 CI = 1.375–7.914) were the only factors associated with current psychosis.

Conclusion: There was a high risk of psychosis in patients with methamphetamine dependence. It was associated with co-morbid affective disorder, antisocial personality, and heavy methamphetamine use. It is recommended that all cases of methamphetamine dependence should be screened for psychotic symptoms.

1. Background

Methamphetamine is a derivative of amphetamine, with more pronounced psychotropic properties [1]. The use of methamphetamine produces a wide range of symptoms, including irritability, physical aggression, hyperawareness and psychomotor agitation. When used in high dose or repeatedly, this stimulant can cause drug-induced psychosis that displays symptoms similar to those of paranoid schizophrenia, which is characterised by hallucinations, delusions and thought disorders.

Methamphetamine-induced psychosis is one of the most widely known side effects associated with high-dose or chronic methamphetamine use [2,3]. An earlier Australian study [4] reported that dependent methamphetamine users were likely to experience psychotic symptoms three times more than their non-dependent counterparts, even after adjusting for history of schizophrenia and other psychotic disorders. In the Pacific region, especially Japan and Taiwan, psychosis as a result of methamphetamine abuse is also common [5,6]. In fact, earlier studies have reported that frequent methamphetamine use increases the risk of psychosis significantly, regardless of whether primary psychotic disorders, such as schizophrenia, are present in the patient [4,7].

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Similar to other stimulants, methamphetamine acts on several sites of the central nervous systems. A unique phenomenon called "behavioral sensitization" or "reverse tolerance phenomenon" was proposed as the mechanism of methamphetamine psychosis [8]. Sensitization developed after repeated use of stimulant; subsequent use of the substance produced intense stereotypy behavior [9], which proposed that dopaminergic supersensitivity was implicated in the development of behavioral sensitization and leading to methamphetamine psychosis. Based on animal studies, chronic administration of methamphetamine increases dopamine release, blocks dopamine reuptake and inhibits monoamine oxidase, resulting in increased level of dopamine, especially in the striatum [9,10]. The vulnerability toward sensitization varies among individuals.

Several risk factors associated with methamphetamine-induced psychosis were reported in previous studies. Familial history of psychotic illness (e.g. familial loading) may increase the risk of developing psychotic symptoms [11]. Those with psychotic disorders are also more likely to have other substance use disorders [12].

Methamphetamine abuse and its psychiatric sequelae are increasingly rampant in Malaysia. In Malaysia, within the first 3 months of 2010, the National Anti-Drug Agency has identified 3611 drug addicts, which is an increase of about 110% for the same period in the previous year. Among these identified addicts, 18% were dependent on amphetamine-type stimulants (ATS), which include amphetamine, methamphetamine and ecstasy pills. This represents a 117% increase in ATS addicts compared with the same period in the previous year [13].

Despite the known risk for both drug-induced and drug-independent psychoses in methamphetamine users, there are no studies on the risk of methamphetamine psychosis and its associated factors in Malaysia. Keeping in view the above-mentioned facts, the present study was aimed to investigate the risk of developing psychosis among methamphetamine-dependent patients and also aimed to observe the associated sociodemographic factors and clinical correlates in Malaysia.

2. Methods

2.1. Study design and subjects

This was a cross-sectional study. To generalize the findings and recruitment rate, this study was conducted at two different centers, namely a teaching hospital (University Malaya Medical Centre) located in the capital of the country (Kuala Lumpur), and a drug rehabilitation center in a suburb city, East Malaysia (Drug Rehabilitation Centre Papar, Sabah). The study was conducted from June 2008 until June 2009.

All patients with methamphetamine dependence were approached during the study period. Patients were briefed on the study and written consent was obtained. Patients who fulfilled the eligibility criteria with urine toxicology screened positive for methamphetamine, and within 30 days of last use of the methamphetamine were included in the study. A face-to-face interview was conducted using a structured questionnaire on drug use behavior and the Mini International Neuropsychiatric Interview (M.I.N.I.) for screening of AXIS I psychiatric disorder and antisocial personality disorder. Lifetime and current methamphetamine-induced psychosis was identified. The interviews were conducted by a qualified psychiatrist.

Inclusion criteria are as follows:

1. Age more than 18
2. Diagnosis of methamphetamine dependence based on DSM-IV
3. Given informed consent

Exclusion criteria are as follows:

1. Those had psychotic symptoms prior to methamphetamine dependence
2. Those with history of schizophrenia or other psychotic disorders.

2.2. Sample size

Sample size was calculated using the computer software EPI-INFO. The estimated prevalence of psychosis in methamphetamine-dependent patient was 21% [4]. A total of 290 subjects were estimated to give the precision of 5% for the study.

2.3. Ethical consideration

Ethical approval was obtained from Medical Ethics Committee of UMMC. Prior to any interview, patients were informed regarding the nature and purpose of the study, and the respondents were given the assurance that all information given will be treated with confidentiality. A written consent was obtained from the patients prior to the interviews.

2.4. Study instruments

2.4.1. Sociodemographic and drug use questionnaire

This was a predesigned questionnaire capturing relevant sociodemographic and clinical variables, which include current age, gender, employment status, total family income, educational level, marital status, and past medical history. Drug use history (duration, amount of money spent per month in Ringgit Malaysia [RM] and route of administration) was also collected (1USD = 3RM).

2.4.2. Mini International Neuropsychiatric Interview (M.I.N.I.)

The M.I.N.I. is a short structured diagnostic interview for DSM-IV or ICD-10 psychiatric disorders for the Major Axis I psychiatric disorder [14]. It has been widely used in international clinical trials and epidemiological studies [15,16]. The MINI was available in local language [17].

2.5. Statistical analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS) Version 16.0. Descriptive analysis

was conducted for the baseline characteristics of the study subjects. Pearson's chi-square test and simple logistic regression were used to examine the association of variables with the occurrence of methamphetamine-induced psychosis. Skewed data were analyzed using appropriate non-parametric test. Significant risk factors in the bivariate analysis were partially adjusted with other significant variables to take care of interactions and confounding effects. Significant variables from bivariate analysis were included for multiple logistic regression analysis. An alpha level of significance 0.05 was set for all analyses.

3. Results

A total of 292 subjects were included in the study, of which 246 were from the drug rehabilitation center, and 46 were recruited from the teaching hospital. The mean age of the subjects was 30.5 years. Subjects from the teaching hospital were about 4 years older. Almost all the subjects were males, except three females who were recruited from the teaching hospital. Most of them were single and Malay with an at least secondary level of education. They mainly had a fulltime job, and one fifth was unemployed. Subjects recruited from the teaching hospital had much higher income than those from the drug rehabilitation center (Table 1).

Table 1
Sociodemographic characteristics of the study subjects (N=292).

Variable	Center of recruitment		Total (N=292)
	Drug rehabilitation center (n=246)	Teaching hospital (n=46)	
Age (years), mean (sd)	29.86 (8.07)	33.80 (8.17)	30.48 (8.20)
Gender, *n* (%)			
Male	246 (100.0)	43 (93.5)	289 (99.0)
Female	0	3 (6.5)	3 (1.0)
Ethnicity, *n* (%)			
Malay	119 (48.4)	30 (65.2)	149 (51.0)
Chinese	33 (13.4)	10 (21.7)	43 (14.7)
Indian	1 (0.4)	6 (13.0)	7 (2.4)
Kadazan	37 (15.0)	0	37 (12.7)
Bajau	56 (22.8)	0	56 (19.2)
Education, *n* (%)			
Primary	47 (19.2)	3 (6.5)	50 (17.1)
Secondary	177 (71.9)	33 (71.9)	211 (72.3)
Tertiary	22 (8.9)	9 (19.6)	31 (10.6)
Employment, *n* (%)			
Full time	194 (78.9)	36 (78.3)	230 (78.8)
Part time	34 (13.8)	2 (4.3)	36 (12.3)
Students	4 (1.6)	2 (4.3)	6 (2.1)
Unemployed	14 (5.7)	6 (13.0)	20 (6.8)
Total income (RM), mean (sd)	1686.0 (1630.6)	5645.4 (15225.0)	2275.1 (6169.2)
Marital status, *n* (%)			
Single	143 (58.1)	20 (43.5)	163 (55.8)
Married	83 (33.7)	20 (43.5)	103 (35.3)
Divorced or widow	20 (8.2)	6 (13.0)	26 (8.9)

More than half of the subjects from either center had polysubstance abuse. Alcohol use disorder was commonly found in subjects from drug rehabilitation center but not from the teaching hospital. About a third of the subjects from the drug rehabilitation center had antisocial personality disorder whereas it was about a quarter in the teaching hospital. Anxiety disorder was not a common co-morbid psychiatric disorder like mood disorder. A fifth of the subjects from the teaching hospital had major depressive disorder, which was slightly higher than the other center. Bipolar disorder was also a common psychiatric co-morbidity seen in both centers (Table 2).

On average, the subjects from the drug rehabilitation center used methamphetamine for more than 6 years while those from the teaching hospital used methamphetamine for only 5 years but with a much higher amount (measured with the money spent per month in Ringgit Malaysia). The common route of administration was smoking. Chase was the second commonest route of administration among the subjects from the drug rehabilitation center but not used by those from the teaching hospital. Other methods of administration were oral, nasal and intravenous (Table 3).

The results in Table 4 show that 140 (47.95%) of the study subjects had past history of a psychotic episode (lifetime methamphetamine-induced psychosis). It was associated with co-morbid major depressive disorder, bipolar disorder and antisocial personality disorder. Lesser amount of methamphetamine use was associated with lower risk of lifetime methamphetamine-induced psychosis. Thirty-eight (13.01%) of the subjects were having current psychosis (current methamphetamine-induced psychosis), and it was only associated with major depressive

Table 2
Psychiatric co-morbidity of the study subjects (N=292).

Psychiatric co-morbidity	Center of recruitment		Total (N=292)
	Drug rehabilitation center (n=246)	Teaching hospital (n=46)	
Mood disorder, *n* (%)			
Major depressive disorder	39 (15.9)	10 (21.7)	49 (16.8)
Bipolar disorder	38 (15.4)	8 (17.4)	46 (15.8)
Anxiety disorder, *n* (%)			
Generalized anxiety disorder	2 (0.8)	0	2 (0.7)
Panic disorder	12 (4.9)	1 (2.2)	13 (4.5)
Social phobia	8 (3.3)	1 (2.2)	9 (3.1)
Obsessive compulsive disorder	3 (1.2)	0	3 (1.0)
Alcohol use disorder, *n* (%)			
Alcohol dependence	77 (31.3)	0	77 (26.4)
Alcohol abuse	51 (20.7)	3 (6.5)	54 (18.5)
Polysubstance abuse, *n* (%)	147 (59.8)	25 (54.3)	172 (58.9)
Antisocial personality disorder, *n* (%)	83 (33.7)	11 (23.9)	94 (32.2)

Table 3
Duration, route and amount of methamphetamine usage among the study subjects (N=292).

	Center of recruitment		Total (N=292)
	Drug rehabilitation center (n=246)	Teaching hospital (n=46)	
Duration (years), mean (sd)	6.68 (5.04)	5.00 (4.30)	6.42 (4.96)
Amount (RM), mean (sd)	912.0 (1630.4)	1395.6 (1716.9)	986.8 (1650.3)
Route, *n* (%)			
Oral	13 (5.3)	5 (10.9)	18 (6.2)
Nasal	3 (1.2)	13 (28.3)	16 (5.5)
Smoking	170 (68.7)	27 (58.7)	197 (67.4)
Intravenous	3 (1.2)	–	3 (1.0)
Chase	58 (23.6)	–	58 (19.8)

RM=Ringgit Malaysia.

disorder and antisocial personality disorder after adjusted for other factors.

4. Discussion

To the best of our knowledge, this was the first study in Malaysia to examine the risk of methamphetamine-induced psychosis among methamphetamine-dependent patients from hospital-based and drug rehabilitation-based populations. A total of 292 methamphetamine-dependent patients were recruited for the study. They were mainly 30-year-old males, having received at least secondary education with fulltime job. This was similar to an earlier study conducted on the demographic characteristics of the Taiwanese individuals [7]. The results of this Taiwanese study showed that usage of methamphetamine was a growing problem in the younger generation of the population.

In the present study, we observed that the risk of current methamphetamine-induced psychosis and lifetime methamphetamine-induced psychosis was 13.01% and 47.95%, respectively. The risk was lower than the result of a cross-country study conducted in Asia-Pacific region, including Australia, Japan, Philippines and Thailand, which reported a much higher prevalence rate of lifetime and current psychotic symptoms [18]. The same study reported that 74.4% of 130 participants were having persecutory delusions followed by auditory hallucinations, strange and unusual beliefs and thought reading during their lifetime. They also found that 44.6% of the participants were having current psychotic symptoms of auditory hallucination.

In contrast, the studies from the West reported lower prevalence compared to our findings. The Methamphetamine Treatment Project [19] reported a 12.9% prevalence rate of current or past psychotic disorders among treatment-seeking, methamphetamine-dependent adults, while a study involving methamphetamine-dependent gay and bisexual men seeking outpatient drug abuse treatment noted a prevalence rate of 26.5% [20]. Another study conducted on inpatients admitted for substance dependence in Sweden showed that 31.5% of methamphetamine abusers met the criteria for psychotic diagnoses [21]. The possible explanation was the use of higher purity of methamphetamine in the Asian region. Alarmingly, according to the reports available from the United Nation Office of Drugs and Crime (UNODC), the use of a high-purity crystalline form of methamphetamine is increasing in the Eastern and Southeastern region of Asia [22].

Methamphetamine users not only are a high-risk population for drug-induced psychosis, but are also at risk for suffering from other psychiatric co-morbidities. Our study demonstrated that methamphetamine-dependent subjects with history psychotic symptoms were significantly associated with higher risk of major depressive disorder, bipolar disorder and antisocial personality disorder.

Substance use in patients with bipolar disorder is common. The National Epidemiological Catchment Area Study (ECA) found a 56% lifetime prevalence of substance abuse or dependence among persons with bipolar disorder [12]. Estroff et al. [23] found that the reported lifetime prevalence of amphetamine abuse in bipolar disorder subject was 38.8%. Although the frequency of this co-occurrence is well documented, the reasons for this association are not clear. There are several potential hypotheses for the association of substance use and bipolar disorders to co-occur. These are as follows: (a) substance abuse occurs as a symptom of bipolar disorder; (b) substance abuse is an attempt by bipolar patients to self-medicate symptoms; (c) substance abuse causes bipolar disorder; and (d) substance use and bipolar disorders share a common risk factor [24].

Our findings of high association of methamphetamine-induced psychosis with major depressive disorder and antisocial personality disorder concurred with the results found in a study by Chen et al. [7]. In the study, their methamphetamine-induced psychosis patients had significantly higher odds of major depression (OR=7.4) and antisocial personality disorder (OR=3.3), when compared with their non-psychotic counterparts. The co-occurrence could also be explained with the hypotheses mentioned for bipolar disorder. Studies have shown that combined abuse of methamphetamine and alcohol can aggravate mental disorders [7,25] because concomitant use of these substances increases toxicity in methamphetamine users, thereby increasing the risk of methamphetamine psychosis. It was also well known that co-morbid alcohol or cannabis use is a common risk of substance-induced psychotic disorder [25] Interaction of amphetamine and alcohol has been reported to increase toxicity in humans and animals [26,27]. However, this association was not replicated in our study. It could be related to the religious background of our study subjects where alcohol consumption is prohibited among the Muslims. Admittedly, the present study did not prove that

Table 4
Analysis of the associated factors with methamphetamine-induced psychosis, lifetime and current.

Variable	Lifetime ($n=140$)			Current ($n=38$)		
	n (%)	Crude OR (95% CI)	Adjusted OR[a,b] (95% CI)	*n* (%)	Crude OR (95% CI)	Adjusted OR[a,c] (95% CI)
Age (years)						
30 and less	84 (48.6)	1.334 (0.808–2.204)	–	23 (13.3)	2.054 (0.873–4.835)	–
More than 30	56 (47.1)			15 (12.6)		
Income (RM)						
2000 and less	96 (43.4)	0.653 (0.362–1.178)	–	20 (9.0)	0.557 (0.244–1.272)	–
More than 2000	44 (62.0)			18 (25.4)		
Ethnicity						
Malay	80 (53.7)	1.430 (0.881–2.321)	–	18 (12.1)	0.488 (0.213–1.117)	–
Non-Malay	60 (42.0)			20 (14.0)		
Education						
Primary	22 (43.1)	0.922 (0.491–1.730)	–	8 (15.7)	2.425 (0.897–6.554)	–
Secondary and above	118 (49.0)			30 (12.4)		
Employment						
Unemployed	15 (75.0)	3.098 (1.051–9.132)	0.940 (0.228–3.931)	6 (30.0)	2.526 (0.741–8.617)	–
Employed or student	125 (46.0)			32 (11.8)		
Marital status						
Single	86 (52.8)	1.905 (1.154–3.144)	1.753 (0.854–3.596)	22 (33.5)	1.721 (0.761–3.893)	–
Married/divorced/widow	54 (41.9)			16 (12.4)		
Major depressive disorder						
Yes	38 (77.6)	4.934 (2.358–10.325)	7.175 (2.612–19.708)	12 (24.5)	2.904 (1.175–7,178)	2.870 (1.154–7.142)
No	102 (42.0)			26 (10.7)		
Bipolar disorder						
Yes	41 (89.1)	13.807 (5.194–36.706)	10.877 (3.167–37.355)	7 (15.2)	1.209 (0.436–3.351)	–
No	99 (40.2)			31 (12.6)		
Anxiety disorder						
Yes	121 (45.7)	0.287 (0.120–0.690)	0.773 (0.212–2.824)	33 (12.5)	0.335 (0.102–1.094)	–
No	19 (70.4)			5 (18.5)		
Alcohol dependence						
Yes	48 (62.3)	3.525 (2.007–6.190)	0.720 (0.205–2.525)	8 (10.4)	2.683 (0.936–7.689)	–
No	92 (42.8)			30 (14.0)		
Alcohol abuse						
Yes	32 (59.3)	2.263 (1.219–4.203)	1.512 (0.444–5.151)	6 (11.1)	1.533 (0.536–4.387)	–
No	108 (45.4)			32 (13.4)		
Polysubstance abuse						
Yes	108 (62.8)	6.363 (3.558–11.379)	1.501 (0.509–4.431)	24 (14.0)	1.518 (0.676–3.410)	–
No	32 (26.7)			14 (11.7)		
Antisocial personality						
Yes	76 (80.9)	12.619 (6.702–23.759)	7.895 (3.366–18.517)	17 (18.1)	3.306 (1.389–7.867)	3.299 (1.375–7.914)
No	64 (32.3)			21 (10.6)		
Duration of methamphetamine use						
6 years and less	59 (37.3)	0.292 (0.174–0.489)	0.819 (0.389–1.722)	21 (13.3)	0.689 (0.308–1.538)	–
More than 6 years	81 (60.4)			17 (12.7)		
Amount of methamphetamine use						
RM1000 and less	82 (36.4)	0.094 (0.044–0.203)	0.144 (0.056–0.374)	25 (11.1)	0.820 (0.347–1.935)	–
More than RM1000	58 (86.6)			13 (19.4)		
Route of methamphetamine use						
Smoking	88 (44.9)	0.739 (0.442–1.237)	–	20 (10.2)	0.533 (0.242–1.173)	–
Other route	52 (54.2)			18 (18.8)		

All the results are adjusted for the center of recruitment.
[a] Only significant variables are included in the multiple logistic regression analysis.
[b] Nagelkerke $R^2=0.626$.
[c] Nagelkerke $R^2=0.353$.

time-dependent or duration of methamphetamine use increases the risk of methamphetamine-induced psychosis as reported in the previous research reports [9,10]. However, our results demonstrated that with a consumption of higher dose of methamphetamine there was a higher risk of developing of lifetime psychosis. This implies a directly proportional dose–response relationship in the development of methamphetamine-induced psychosis. This relationship was previously observed in association between cannabis and psychosis [28].

5. Conclusion

The risk of psychosis among methamphetamine-dependent subjects was high in Malaysia. The associated factors for psychosis in methamphetamine-dependent patients were co-morbid affective disorder, antisocial personality and higher amount of methamphetamine use. The findings of this study provide important insights into methamphetamine-induced psychosis, and will impart a clearer understanding and help the mental health care providers to formulate effective treatment and management of severe and persistent mental illnesses that co-occur with methamphetamine use. A longitudinal and prospective study could be done in the future in order to investigate any causal relationship, onset, course and outcome.

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