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Risks of psychosis in methamphetamine users: cross-sectional study in Thailand

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ABSTRACT

Objective To determine factors related to recent methamphetamine-associated psychosis (MAP) among individuals recently using methamphetamine (MA).

Design Cross-sectional study carried out between July 2015 and June 2017.

Setting Four mental health hospitals and one substance abuse treatment centre in Thailand.

Participants Individuals recruited onto the study included those aged 18 years or over, of both sexes, who reported MA use in the month prior to admission.

Measures Any recent psychosis was confirmed using the Mini International Neuropsychiatric Interview-Plus psychotic module. The Timeline Follow Back was used to determine days of MA use. The severity of MA dependence was assessed using the Severity of Dependence Scale. Quantitative hair analysis was carried out to confirm recent use of MA and to measure the amount of MA use. We compared several characteristics between those who had recently experienced psychosis and those who had not.

Results This study included 120 participants without MAP and 113 participants with MAP. The mean age was 28 years and the mean abstinence was 17 days. The levels of MA concentration in hair were not significantly different between groups (p=0.115). Based on the final logistic regression model, the independent factors associated with MAP (OR and 95% CI) included being male (OR 4.03, 95% CI 1.59 to 10.20), ≥16 days of MA use in the past month (OR 2.35, 95% CI 1.22 to 4.52), MA dependence (OR 9.41, 95% CI 2.01 to 44.00) and hospitalisation history related to substance abuse (OR 3.85, 95% CI 2.03 to 7.28).

Conclusions Health professionals should closely monitor the development of MAP in MA-dependent men who frequently use MA and have a history of hospitalisation for substance abuse. The measure of MA concentration levels in the hair may add no benefit for the prediction of the development of MAP.

Strengths and limitations of this study

► This study examined risks of recent methamphetamine-associated psychosis (MAP) in a clinical sample in which there was recent use of methamphetamine (MA).

► This study used MA concentration levels in the hair to confirm recent MA use and to determine the amount of MA use.

► This study used a structure clinical interview for diagnosis to confirm a recent diagnosis of substance-induced psychotic disorder.

► This is a cross-sectional study.

► Some risks of MAP were not included in the study, for example, polydrug use; history of conduct disorder, depressive and anxiety disorders; premorbid schizoid/schizotypal personality trait; family history of psychotic disorders; family history of schizophrenia; and bipolar disorder.

and 46% of MA users are likely to develop psychosis at least once in a lifetime.[3] Based on these estimations, MAP may currently affect millions of people around the world.

The symptoms of MAP are similar to those of schizophrenia and are associated with serious negative consequences. Its common symptoms include auditory hallucinations, visual hallucinations, strange or unusual beliefs, persecutory delusion and negative psychotic symptoms, which cannot be distinguished from schizophrenic psychotic symptoms.[4 5] These psychotic symptoms usually cause anxiety, fear, terror and decreased behavioural control. A case of severe psychosis can lead to unpredictable episodes of aggression and violence. Previous studies found that MA users with psychotic symptoms had a higher risk of violent behaviour than MA users who had no psychotic symptoms.[6] Other than the more frequent use of health services and attempted suicide, MA users with MAP are more likely to have medical, employment and legal problems than those without MAP.[7] The findings from long-term studies also suggest that 25%–38% of individuals with

INTRODUCTION

Methamphetamine-associated psychosis (MAP) is an increasing health problem. Amphetamines are one of the most common drugs used in East and Southeast Asia. In 2016, an estimated 34.2 million people worldwide used amphetamines in the past year.[1] In its class, methamphetamine (MA), a very potent amphetamine derivative, is the most frequently used substance.[2] Between 21%

MAP may develop primary or persistent psychosis sometime in later life.[8 9]

Because a subset of MA users may develop psychotic symptoms, important questions are raised about MA users who may have an increased risk of MAP. Previous studies suggest that MAP is associated with a number of MA use patterns and psychiatric comorbidities. In early Japanese studies in which most users exclusively used MA (1955–1992), the investigators found an association between frequent and long-term use of MA and MAP.[10] Based on a recent review, replicated risks factors included early-age MA use, frequent and long-term use of MA, MA dependence, alcohol and other drug use, major depressive disorders and antisocial personality disorders.[11] That review found no association between sociodemographic factors and MAP. In addition, some risk factors are not yet clear, for example, other drug use, psychiatric comorbidity, family history of psychiatric illness and childhood trauma.

Despite the increasing evidence around risk factors of MAP, there are some limitations in previous studies. First, many studies were carried out using patients with a lifetime history of MA use and/or MAP. The results of these studies may be less reliable because the participants may not have been able to recall those experiences accurately. Second, some of them did not exclude individuals with primary psychotic disorders prior to MA use. Lastly, most studies did not use a valid method to confirm or measure the amount of MA use. For these reasons, we proposed to carry out a cross-sectional study to determine the risk of psychosis in Thai people who recently used MA and had recently experienced MAP. This studied population was chosen to minimise the problems of inaccurate recalls on MA use and MAP experience. We hypothesised that a number of patients' characteristics, including the amount of MA in the hair of the users, should be used as predictors of MAP.

METHODS

This cross-sectional study was carried out in MA users admitted to four mental health hospitals and one substance abuse treatment centre in Thailand. Suanprung Psychiatric Hospital and Thanyarak Chiang Mai Hospital are located in Northern Thailand. Nakhon Phanom Rajanagarindra Psychiatric Hospital is located in Northeastern Thailand. The Galyarajanagarindra Institute is located in Central Thailand. Songkhla Rajanagarindra Psychiatric Hospital is located in Southern Thailand. This study was carried out between July 2015 and June 2017.

Participants

We assessed 120 MA users with MAP and 120 MA users without MAP. Participants included those aged 18 years or over, of both sexes, with self-reported MA use at least once in the month prior to admission. The primary reasons for their hospitalisation were MAP and/or MA use disorders. The Mini International Neuropsychiatric

Interview (MINI)-Plus psychotic module, was used to confirm a recent diagnosis of substance-induced psychotic disorder.[12] Based on the data elicited from this module, participants who developed psychosis prior to substance use and due to a general medical condition were excluded from the study.

Assessment

All clinical assessments were completed in a single day. As a cross-sectional study, this study had no follow-up visit. We assessed the participants when they were less likely to harm themselves or others. Apart from sociodemographic data, we interviewed each participant to elicit the pattern and history of MA use. We assessed the severity of depression and MA withdrawal using the nine-item Patient Health Questionnaire (PHQ-9) and the Amphetamine Withdrawal Questionnaire (AWQ).[13 14] The Timeline Follow Back was used to determine days of MA use.[15] The severity of MA dependence, current psychotic symptoms and cognitive impairment were assessed using the Severity of Dependence Scale (SDS),[16] the 18-item Brief Psychiatric Rating Scale (BPRS)[17] and the Montreal Cognitive Assessment (MoCA),[18] respectively. We confirmed any diagnosis of alcohol and other substance use disorders and antisocial personality disorder using the MINI alcohol use disorder, substance use disorder and antisocial personality disorder modules, respectively.[12] In addition, the MINI suicidality module was also used to assess the level of suicidal tendency.

Hair was collected from each participant during hospitalisation. Scalp hair was cut close to the scalp from the vertex posterior region, with root ends marked, and was kept in a clean plastic bag. The bag was then sealed with aluminium foil paper and shipped to the Department of Forensic Medicine, Chiang Mai University, for quantitative hair analysis. The analysis for hair MA levels followed a previously published protocol involving solid-phase microextraction in line with gas chromatography/mass spectrometry.[19] Derivatising reagents for hair analysis were heptafluorobutyric chloride (98% purity) and heptafluorobutyric anhydride (99% purity). Both reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA). The limit of detection and the limit of quantitation for the present analysis were 0.10 and 0.15 ng/mg of hair, respectively.

MA concentration levels in the hair was the primary outcome measure. Other measures were considered as the secondary outcomes.

Statistical analyses

Our sample size calculation was based on the number of events per variable (NEV) in logistic regression analysis. We hypothesised that a maximum of 10 variables might be included in the final model of logistic regression analysis. In 1996, Peduzzi and colleagues have proposed that a logistic regression model with an NEV of 10 or more would be less biassed.[20] In this study, we planned to enrol at least 100 patients with MAP and 100 patients without

MAP. To compensate for some participants with incomplete data, we decided to enrol 120 patients for each group.

All missing data were considered as not available data. We present each variable as percentage, mean and/or SD. The association between each potential factor and MAP was assessed using a univariate analysis, including the χ^2 test for categorical data for all cell sizes >5, the Fisher exact test for categorical data for a cell size ≤5 and the Student t-test for continuous data. Manual backward elimination, binary logistic regression analysis was used to identify the independent risks that showed a significant correlation with MAP. The first regression model included all univariate variables significantly correlated with MAP (p≤0.05). The variable with the highest p value of each regression model was then eliminated step by step. Only the risks significantly predicting MAP (p<0.05) were included in the final regression model. ORs with corresponding 95% CIs and β's were used to estimate the associations of nominal and continuous variables with MAP, respectively. The Hosmer and Lemeshow (H–L) test was applied, and its p value of 0.05 or higher indicated that the model fitted well with the data. The variance inflation factors (VIFs) of each variable included in the final model were computed, and a VIF of >10 indicated that multicollinearity of the corresponding variable was high.[21] A p value of <0.05 indicated a significant prediction. All reported p values are two-sided.

All statistical analyses were done using R V.3.5.1.[22] We used the Rcmdr V.2.4–4 for univariate and multivariate analyses, the RcmdrPlugin.ROC V.1.0–18 for testing the H–L goodness of fit (GOF) and the rcompanion V.1.13.2 for calculating the Nagelkerke R^2.[23–25]

Patient and public involvement

Participants were not directly involved in the design of the study. The main results will be communicated to health professionals, who may need some predictors of MAP in their clinical practice.

RESULTS

The total numbers of participants were 120 with MAP and 120 without MAP. Of the 120 participants with MAP, 7 were excluded because their hair tests were negative for MA.

The data of 233 participants were included in the analysis. The whole sample included 201 men and 32 women who had a mean age (SD) of 28.3 (7.2) years, a mean of days since last use (SD) of 16.80 (9.27), a mean PHQ-9 score (SD) of 6.8 (4.5) and a mean AWQ score (SD) of 7.3 (5.4).

The mean BPRS score (SD) of the MAP group was 25.42 (6.47). Table 1 shows the demographic data and characteristics of both groups. The mean values (SD) of MA concentration levels in the hair of the MAP group (13.68 ng/mg (25.95)) and that of the no-MAP group (8.93 ng/mg (24.66)) were not significantly different

(p=0.115). The MA concentration levels in the hair and the BPRS scores were not significantly correlated in both the MAP group (Spearman's r=0.160, p=0.091) and in the no-MAP group (Spearman's rho=0.031, p=0.736). The mean (SD) MoCA scores of the MAP group (24.95 (2.96)) and the no-MAP group (25.77 (3.23)) were significantly different (p=0.046).

The univariate analysis revealed the association of MA psychosis and eight factors, including being male, MA dependence, antisocial personality disorder, history of hospitalisation for mental illnesses, history of hospitalisation for substance abuse, intravenous use in the past month, MA use for ≥16 days in the past month and younger age at first use (p<0.05) (see table 1). These eight factors were independent variables included in the first binary logistic regression analysis. After four steps of manual elimination of non-significant predictors, the final model included four risks that significantly predicted MA psychosis. These were being male, MA dependence, history of hospitalisation for substance abuse and MA use for ≥16 days in the past month (p<0.05) (see table 2). The H–L GOF test indicated no evidence of poor fit (χ^2=1.39, df=8, p=0.99). The VIFs of all four predictors were between 1.02 and 1.05.

DISCUSSION

This study examined risks of MAP in a clinical sample in which there was recent use of MA. The recent MA use and recent MAP were confirmed by using hair analysis and MINI-Plus, respectively. The low BPRS scores (mean=25.42) of the MAP group suggested that they were assessed after the recovery from psychosis. Risks of MA psychosis included being male, meeting the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) diagnosis of MA dependence, history of hospitalisation for substance abuse and using MA for ≥16 days in the past month. However, the amount of MA use measured by hair analysis was not related to experience of MA psychosis.

Although there have been many studies on the risks of MAP, only a few of them were carried out in MA users with a recent history of psychosis.[26–28] Although the mean level of hair MA in the MAP group was higher, the differences of these levels were not significant between groups. This finding was in contrast with that of a previous study reporting the association between the amount of MA use and lifetime diagnosis of MAP.[29] Similar to the findings from two previous studies,[27 28] we did find a correlation between the frequency of recent MA use and the development of MAP. However, the previous and the present studies differ on at least two respects. While the previous studies assessed the association between self-reported MA use and lifetime MAP, our study examined the correlation between hair MA levels and recent MAP. If any future study confirms the present findings that frequency but not the amount of MA use predicts MAP, it would mean that frequency is more important than the amount of MA use in predicting MAP.

Table 1 Demographic and clinical characteristics of MA users with and without psychosis

	MA users without psychosis (n=120)	MA users with psychosis (n=113)	Statistical analysis
	n (%)	n (%)	χ^2/Fisher's exact test
Gender: male	95 (79.2)	106 (93.8)	χ^2=9.33, p=0.002
MA use disorder			
Abuse	18 (15.0)	2 (1.8)	OR=9.72, p<0.001
Dependence	102 (85)	111 (98.2)	
Comorbid alcohol use disorder (including lifetime)	52 (43.3)	54 (47.8)	χ^2=0.303, p=0.582
Comorbid cannabis use disorder (including lifetime)	25 (20.8)	33 (29.2)	χ^2=1.756, p=0.185
History of intravenous drug use	4 (3.3)	5 (4.4)	OR=1.34, p=0.743
History of suicide attempt	10 (8.3)	17 (15.0)	χ^2=1.95, p=0.163
Antisocial personality disorder	13 (10.8)	27 (23.9)	χ^2=6.09, p=0.014
History of hospitalisation for mental illnesses	1 (0.8)	11 (9.7)	OR=12.73, p=0.002
History of hospitalisation for substance abuse	24 (20)	52 (46)	χ^2=16.76, p<0.001
Most common route of MA use in the past month			
Smoking	120 (100.0)	107 (94.7)	OR=0.0, p=0.012
Intravenous use	0 (0.0)	6 (5.3)	
≥16 days of MA use in the past month	23 (19.2)	41 (36.3)	χ^2=7.72, p=0.005
	Mean (SD)	**Mean (SD)**	**Student t-test**
Age (years)	27.80 (7.72)	28.75 (6.65)	t=1.006, p=0.316
Age at first MA use (years)	19.04 (5.83)	17.65 (4.31)	t=2.068, p=0.040
Severity of dependence (SDS score)	4.70 (2.34)	5.08 (2.38)	t=1.227, p=0.221
Cognitive function (MoCA score)	25.77 (3.23)	24.95 (2.96)	t=2.01, p=0.046
MA concentration levels in hair (ng/mg)	18.93 (24.66)	13.68 (25.95)	t=1.582, p=0.115

MA, methamphetamine; MoCA, Montreal Cognitive Assessment; SDS, Severity of Dependence Scale.

This study assessed MA dependence using two measures, the SDS and the DSM-IV diagnosis of MA dependence. Our finding that MA-dependent users had a higher risk of MAP than an MA abuser confirms a previous report.[30] In another study, the investigators found a correlation between MAP and MA dependence, defined by using an SDS score of 4 or more.[28] However, our study did not find a difference in SDS scores between groups. The discordance between the diagnosis of MA dependence and SDS scores may reflect that these two measures assess different aspects of MA dependence. The present finding that the history of hospitalisation for substance use could predict MAP appears to be in concordance with the predictability of MA dependence. Taken together, the SDS should be used with caution in future clinical studies of MAP.

Although a literature review did not find any correlation between sociodemographic characteristics and MAP,[11] our study and previous studies did find that male MA users were more likely to experience MAP.[27] As two diseases in the same continuum,[31] the higher risk of MAP

Table 2 Manual backward elimination and binary logistic regression analysis to determine the risk of MA psychosis

Risk factor	β	SE β	OR (95% CI)
Intercept	−4.05***	0.91	0.02 (0.00 to 0.10)
Male (vs female)	1.39**	0.48	4.03 (1.59 to 10.20)
MA dependence (vs MA abuse)	2.24**	0.79	9.41 (2.01 to 44.00)
History of hospitalisation for substance abuse (vs no history)	1.35***	0.33	3.85 (2.03 to 7.28)
≥16 days of MA use in the past month (vs ≤15 days in the past month)	0.86*	0.33	2.35 (1.22 to 4.52)

Nagelkerke R^2 (Cragg and Uhler)=0.26. Hosmer and Lemeshow goodness of fit test: χ^2=1.39, df=8, p value=0.99.
*p<0.05, **p<0.01, ***p<0.001.
MA, methamphetamine.

in men appears to be in line with the findings that men are more likely than women to develop schizophrenia.[32]

To our knowledge, this is the first study using hair analysis to confirm recent MA use and to determine the amount of MA use. By using this objective test, we excluded the data of 11 participants with negative results of hair analysis. The amount of MA use measured by hair analysis in this study should be more accurate than that calculated based on self-reporting.[29] The recent MAP diagnosed in this study was also confirmed using the MINI-Plus psychotic module, which is a structure clinical interview widely used for diagnosis. By using the logistic regression, the predictors found in this study had already been adjusted by multiple variables.

This study has several limitations. First, only few women, intravenous users, and those with a history of hospitalisation for mental illnesses participated in this study. The present findings, therefore, could not apply in these populations. Second, the Nagelkerke R^2 (Cragg and Uhler) of 0.26 suggested that these four variables could explain 26% of the variance, which implied that some risks of MAP were not included in the study. Examples of risks reported in previous studies but not included in the present study are polydrug use[26]; history of conduct disorder, depressive and anxiety disorders[27]; premorbid schizoid/schizotypal personality trait[29]; family history of psychotic disorders[27]; and family history of schizophrenia and bipolar disorder.[33] Not only patients with transient MAP but also the relatives of patients with persistent MAP had a higher prevalence rate of schizophrenia compared with relatives of patients with transient MAP.[34] Third, as a cross-sectional study, we could not confirm that the group without MAP would not develop a psychotic illness at a later point in time. Fourth, the group without MAP that participated in this study included MA users who were hospitalised due to MA use disorder. As heavy users of MA, this comparison group, therefore, might not be much different from the MAP group. Fifth, some important data were not recorded, for example, the frequency of hospitalisations, the period of time between last MA use and the hair collection. Finally, based on the MoCA scores, the participants in this sample appeared to have mild cognitive impairment, which might affect the accuracy of reported data. Although the MoCA scores of the MAP group were significantly lower than those of the no-MAP group, we did not include this variable in the logistic regression model. This decision was made because the poorer cognition in the MAP group might not be a risk but might be a consequence of MAP.

Health professionals should closely monitor the development of MAP in MA-dependent men who frequently use MA and have a history of hospitalisation for substance abuse. The measure of MA concentration levels in the hair may add no benefit for the prediction of the development of MAP. Future studies on the correlation between the amount of MA use and the development of MAP are warranted.

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