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Pattern of Methamphetamine Use and the Time Lag to Methamphetamine Dependence

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Abstract

Objectives—Use of methamphetamine (MA) commonly co-occurs with the use of other substances. The present study aims to examine substance initiation patterns of other substances, including alcohol, nicotine, inhalants, and cannabis (OTH), in MA users and its consequence on the time lag of MA dependence.

Methods—Socio-demographic, environmental, and clinical data were obtained from MA users at a Thai substance treatment center. The Semi-Structured Assessment for Drug Dependence and Alcoholism was employed to diagnose drug dependence.

Results—Of 991 MA users, 52.6% were males, and the average age was 26.8±7.1 years. The mean age of first MA use (18 years) was greater than the mean age of first use of alcohol (17 years), nicotine (16 years), and inhalants (15 years) ($p<0.001$), but was comparable to the mean age at the first use of cannabis ($p>0.05$). Family history of MA use and nicotine dependence were associated with early MA onset. Participants who used MA as their first drug (MA>OTH) were more likely to be female and less likely to smoke intensely and to be exposed to severe traumatic events than those who used MA later than other substances (OTH>MA). The time lag from age at onset of MA use to MA dependence was shorter in OTH>MA than in MA>OTH (3 years vs. 5 years; $\chi^2=5.7$, $p=0.02$, log-rank test).

Conclusions—A higher proportion of women was observed in MA>OTH than in OTH>MA. The use of other substances prior to MA increases the individual's vulnerability in shortening the interval between age at onset of MA use and MA dependence in a substance treatment cohort.

Keywords

Methamphetamine; alcohol; nicotine; cannabis; inhalants; pattern of use

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1. Introduction

The use of amphetamine-type stimulants (ATS), including methamphetamine (MA), is rapidly increasing. Over the past decade, ATS seizures have quadrupled worldwide to 144 tons in 2012, although a slight decrease was observed in 2013 (UNODC, 2015). Most ATS were seized in North America and East and Southeast Asia (Embry et al., 2009; UNODC, 2014, 2015). US studies have reported an 8.6% lifetime prevalence of MA use in a population sample of 18 to 49 years of age (Durell et al., 2008). In Thailand, the prevalence of MA use among the Thai population between 18 and 64 years of age has been approximately 1.7% to 1.9% in recent years, ranking Thailand among the top countries in the world in MA prevalence. MA use is often associated with neuropsychiatric illnesses (Kalayasiri et al., 2010; Kalayasiri et al., 2014; McKetin et al., 2006) and medical illnesses (Ito et al., 2009; Sadeghi et al., 2012). Moreover, MA use commonly co-occurs with other substance use disorders, such as alcohol, nicotine, and/or illegal substances (Brecht et al., 2007; Yen et al., 2005).

Many studies worldwide have examined the differences in the sequence of substance use initiation between hard and soft drugs, alcohol, and nicotine. Thus, it has been proven that most individuals who use cocaine or heroin started with other substances (Guerra et al., 2000; Navaratnam and Foong, 1989; Sartor et al., 2014). These results might be interpreted as evidence for the gateway hypothesis proposed by Denise Kandel (Kandel et al., 1992), which suggests that there is a sequential pattern of drug use. However, psychosocial and environmental factors may better explain such findings regarding the sequence pattern of substance ‘*initiation*’ (i.e., by peer pressure, personal experimentation or lack of self-control, drug availability, or the legal system). For example, a family history of drug use was associated with early MA onset in men (Messina et al., 2008). Early exposure to childhood adverse events was associated with early substance use (Whitesell et al., 2009) or MA onset in both males and females, although females were more likely to have a higher rate of childhood adverse events than males (Messina et al., 2008). Moreover, although patterns of substance use differ between males and females, the differences are not the same across different cultures. Therefore, the pattern of substance use initiation should be monitored periodically (Castaldelli-Maia et al., 2014; Reid et al., 2007).

There are fewer data on the sequence of substance use initiation for MA use than for cocaine or heroin use. A population-based study in Brazil found that inhalants were used prior to the ATS among university students (Castaldelli-Maia et al., 2014). Studies in Taiwan and the U.S. found that nearly all (95–96%) of the MA users used nicotine or alcohol before they started to use MA (Brecht et al., 2007; Yen et al., 2005). Male, but not female, MA users with early-onset MA use were more likely to use alcohol prior to MA than those with late-onset MA use (Yen et al., 2005). To our knowledge, although a population-based approach has been used, no human studies have examined the sequence of substance use prior to the use of MA and the effects of other substance use prior to MA use on the occurrence of MA dependence or time lag to MA dependence. We therefore examined the pattern of substance use initiation in the treated MA use cohort, a highly selective sample with experienced MA use, in order to partly answer the above research questions (particularly time lag to MA

dependence) as individuals with MA dependence were selectively pooled in the treatment setting.

Predictors of the sequence of MA use as compared to other substances include alcohol, nicotine, cannabis, and inhalants (OTH) in terms of demographics, diagnoses, and environment. The predictors of early/late-onset MA use and the effects of using other substances prior to MA on the time lag between MA use and MA dependence were explored using part of the data from the genetic study of MA dependence and paranoia (Kalayasiri et al., 2014). The results may provide basic knowledge regarding the pattern of MA use, at least in people living in substance treatment settings, and may be used as a public education tool regarding the associations between the use of alcohol, nicotine, and soft drugs and the vulnerability to a hard drug such as MA.

2. Methods

2.1 Subjects

Socio-demographic, clinical, and MA-related variables were obtained using the Thai version of the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA) (Kalayasiri et al., 2014; Malison et al., 2011) as part of the genetic study, which collected data in 4-month-hospitalized MA-dependent patients between 2007 and 2011 at the Thanyarak Institute on Drug Abuse in Pathumthani, Thailand. The study protocols are described in detail elsewhere (Kalayasiri et al., 2010; Kalayasiri et al., 2014). Briefly, individuals aged 18 years or above and with more than 10 episodes of MA use in their lifetime were included. Patients with primary psychotic disorders or neurological disease (e.g., cerebrovascular disease, epilepsy) were excluded. The study was approved by the ethics Committees of the Faculty of Medicine of Chulalongkorn University (Med Chula IRB), Thanyarak Institute for Drug Abuse, and the Thailand Ministry of Public Health.

2.2 Measurement

The SSADDA is a comprehensive interview employed to diagnose the use of various substances, substance dependence, and mental disorders based on the DSM-IV (Pierucci-Lagha et al., 2007). The SSADDA was translated into Thai and shows a high inter-rater/inter-instrument reliability (Kalayasiri et al., 2014; Malison et al., 2011). Rigorous quality control data, i.e., 10 practice interviews and cross-edits, were obtained on this version of the SSADDA interview that was administered by trained interviewers (all with bachelor's degrees or higher in psychology/mental health). Age at onset of MA, nicotine, alcohol, cannabis, and inhalant use was obtained at the beginning of each SSADDA section. Early MA onset was determined when the age at onset was ≤ 15 years. "Dependence", as used in this study, is based on the diagnostic criteria for substance dependence from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Individuals with MA dependence were asked when they first experienced 3 or more DSM-IV criteria within a 12-month period, which was also the diagnostic criterion for MA dependence used in the study. The sequence of substance use was categorized into two groups: a) first MA and later other substances (labeled as MA>OTH); and b) first use of substances other than MA and later MA (labeled as OTH>MA).

We collected data on traumatic events experienced by the patients as a possible environmental variable and MA family history as environmental and/or genetic variables associated with MA use (Messina et al., 2008; Yen et al., 2005). The Environment section in the Thai SSADDA was used to assess participants' childhood traumatic experiences and was first reported here. All the participants were asked whether they had witnessed or experienced a violent crime or had been sexually abused by 13 years of age. The diagnosis of antisocial personality disorder is based on the DSM-IV (Glasner-Edwards et al., 2010; Ogloff et al., 2015). Variables (e.g., demographics: age, sex; diagnoses: other substance dependence, antisocial personality disorder) known to be associated with MA use were chosen from the previous report (Kalayasiri et al., 2014).

2.3 Statistical analysis

Visual inspection and the Kolmogorov-Smirnov test were used to check normality of distribution, and data were log transformed if not normally distributed. Age at onset was compared between MA and OTH using Wilcoxon signed-rank tests. Differences in socio-demographic and clinical data between the MA>OTH versus OTH>MA groups and early-onset versus late-onset MA use groups were compared using analyses of contingency tables (chi-squared [χ^2] tests) and binary logistic regression analyses (forward likelihood ratio method; variables included in the analysis were chosen when the p values are lower than 0.1 from χ^2 tests). Kaplan-Meier survival analyses were used to examine time from MA first use to MA dependence onset. Log-rank tests were used to compare median survival time between the MA>OTH and OTH>MA groups.

3. Results

Of 991 MA users, 521 (52.6%) were males, and 146 (14.7%) were married. The average years of education was 8.1 ± 2.9 , and the average age at enrollment was 26.8 ± 7.1 years. Of the 991 participants, 956 (96.5%) used nicotine, 955 (96.4%) used alcohol, 180 (18.2%) used cannabis, and 111 (11.2%) used inhalants. The prevalence of lifetime MA dependence was 73.6%, nicotine was 59.9%, alcohol was 23.6%, cannabis was 5.4%, and inhalants were 5.5%. Table 1 shows the mean age at onset of MA, nicotine, alcohol, cannabis, and inhalants use and dependence. Age at onset of MA use was greater than that of nicotine (18.5 ± 5.5 vs. 16.2 ± 4.2 ; $p < 0.001$), alcohol (18.6 ± 5.6 vs. 17.0 ± 4.2 ; $p < 0.001$), and inhalants use (18.2 ± 5.4 vs. 15.4 ± 3.5 ; $p < 0.001$), but did not differ from that of cannabis use (18.0 ± 6.3 vs. 17.1 ± 3.5 ; $p = 0.39$).

Table 2 shows the differences between the OTH>MA and MA>OTH groups. There were significant differences ($t_{989} = 11.9$, $p < 0.001$) in age at onset of MA use between individuals in the MA>OTH group (16.2 ± 3.4 years) and the OTH>MA group (19.9 ± 6.1 years). MA users in the MA>OTH group were more likely to be female ($\chi^2_1 = 14.0$, $p < 0.001$) and to have a family history of MA use ($\chi^2_1 = 4.6$, $p = 0.04$), and were less likely to have traumatic event exposure ($\chi^2_1 = 4.7$, $p = 0.03$) and to be dependent on alcohol ($\chi^2_1 = 11.2$, $p < 0.001$), nicotine ($\chi^2_1 = 9.2$, $p = 0.002$), and cannabis ($\chi^2_1 = 4.8$, $p = 0.03$) than individuals in the OTH>MA group. Table 2 also shows that individuals with early-onset MA were more likely to have a

family history of MA use, antisocial personality disorder, and nicotine and cannabis dependence than those with late-onset MA ($p<0.05$, two-tailed χ^2 test).

Table 3 shows the results of a binary logistic regression analysis with use of MA as the first substance used as the dependent variable (reference group: MA was not the first substance used) and another binary logistic regression analysis with early-onset MA use as the dependent variable. Being female (adjusted odds ratio [OR]=1.84, $df=1$, $p<0.001$) was significantly associated with MA use as the first substance, while individuals with nicotine dependence (adjusted OR=0.64, $df=1$, $p=0.001$) and those who were exposed to severe traumatic life events (adjusted OR=0.67, $df=1$, $p=0.01$) were less likely to use MA as the first substance (Wald₁=7.4, $p<0.001$; Nagelkerke $R^2=0.074$). There was a significant positive association between early-onset MA use and a family history of MA and nicotine dependence (Wald₁=152.65, $p<0.001$; Nagelkerke $R^2=0.053$).

As shown above, 729 (73.6%) out of 991 MA users had MA dependence. The time lag (median survival time) between age at onset of MA initiation to MA dependence was 3.0 years (standard error = 0.2, 95% confidence interval = 2.4–2.5). The figure shows the differences in time lag (survival time) from MA initiation to MA dependence between the OTH>MA and MA>OTH groups. OTH>MA individuals had a shorter median survival time to become dependent than individuals in the MA>OTH group (median survival time = 3.0 years, standard error [S.E.] = 0.24, 95% confidence interval [CI] = 2.5–3.5 versus median survival time = 5.0 years, S.E.=0.4, 95% CI = 4.2–5.8; $\chi^2=5.7$, $p=0.02$, log-rank test).

4. Discussion

To our knowledge, this study is the first study in humans to investigate the association between the time lag from age at onset of MA use to MA dependence and the pattern of MA and other substance use. As expected, the age of first MA use was later than those of nicotine, alcohol, and inhalants use, but comparable to that of cannabis use. Family history of MA use and nicotine dependence predicted early MA onset, while female gender, non-nicotine dependence, and non-exposure to severe traumatic events predicted using MA as the first substance. The time lag between the first use of MA and MA dependence was shorter in participants who used other substances prior to MA than those who used MA as their first drug.

Age at onset of MA use occurred later than that of other substances. This is in agreement with previous data (Brecht et al., 2007; Reid et al., 2007; Yen et al., 2005). These results may be explained by MA legislation. MA is illegal in most countries around the world unlike alcohol or nicotine, which can be sold legally and are easily accessible. Thus, our findings are not sufficient to support the classical gateway hypothesis regarding the sequence of substance ‘*initiation*’ (Kandel et al., 1992; van Leeuwen et al., 2011). It is also important to note that the age of onset of cannabis use was comparable to that of MA. As of 2017, cannabis is scheduled as a Class 5 substance in Thailand’s Narcotic Act, which prohibits any cannabis use in the kingdom. This policy might help in delaying the age of cannabis initiation in Thailand.

Although our results indicate that nicotine exposure or dependence may be a predictor of early onset of MA use, which is in accordance with the results of a previous study (Moss et al., 2014), this should not be interpreted as a causal relationship. In fact, the OTH>MA group had a later age of MA onset than the MA>OTH group. Importantly, the time difference between the first use of MA and MA dependence was 3.0 years. Knowing the time lag may allow authorities to provide proper interventions to prevent the development of dependence. Nevertheless, the result of a shorter lag to MA dependence found in OTH>MA than in MA>OTH may be due to differences in the age of onset, age at the time of study, or gender difference between these groups. However, the fact that the MA>OTH group had a younger age of MA use onset and younger age at the time of the study precluded such an assumption, although there was no difference in MA use duration compared to the OTH>MA group.

Participants who used MA as the first substance were more likely to be female and less likely to have nicotine dependence. Previous studies have found that sex is associated with the risk of initiation to MA and heroin (Fattore et al., 2014; He et al., 2013; Shand et al., 2011). Females have previously been found to use MA or cocaine (Sartor et al., 2014; Yen et al., 2005) more frequently as the first substance compared to males. This may be explained by biological differences (Anker and Carroll, 2011; Fattore et al., 2014) or psychosocial aspects of substance use. Previous studies have also found that comorbidity of depression was present in female MA users (Dluzen and Liu, 2008; Yen and Chong, 2006), suggesting that MA may serve as a type of self-medication for women. In a population-based study conducted in Northern Thailand, female gender and younger age were associated with higher depressive symptoms (DiMiceli et al., 2016). Likewise, exposure to childhood adverse events, an environmental factor associated with early-onset MA use, is found commonly in female MA users (Messina et al., 2008). However, our finding of fewer exposures to traumatic events in individuals who used MA as the first substance (see below) precludes such a conclusion. We speculate that the role of men who used MA may influence the initiation of women's MA use. In addition, social concern may be used as an explanation because women, especially in the Asian context, are expected to be aware of misdemeanors, which is consistent with previous studies that females were less likely to use other substances (He et al., 2013; Hser et al., 2005). These findings not only highlight the need for consideration of gender when assessing MA use, but can also serve to focus on the prevention and treatment programs that address the different specific needs of men and women.

Exposure to traumatic events is common among individuals with substance use disorders (Giordano et al., 2014; Walsh et al., 2014). Early exposure to adverse events was associated with early substance use and the subsequent development of substance use disorder (Messina et al., 2008; Whitesell et al., 2009). Because legal substances such as nicotine and alcohol are more easily accessible than controlled substances such as MA, persons with severe traumatic exposure may have a greater chance of initiating with alcohol or nicotine prior to MA use (Walsh et al., 2014). In addition, our data support the idea that individuals who used MA as the first substance may be more likely to have a stable life than MA users who used MA later than other substances. Therefore, the two groups (MA>OTH vs OTH>MA) might have different issues at the time of each substance initiation. For example,

individuals who used MA as the first substance may use it for recreational reasons or to increase their performance, while those who used MA later than other substances may start using substances because of stressful life events. We suggest further study of this hypothesis.

Family history of MA use was a predictor of an early onset of MA use, which is consistent with previous studies (Messina et al., 2008; Saldana et al., 2013); furthermore, antisocial personality disorder was associated with early onset of MA use in the initial analysis. These associations may be explained by both genetic and environmental factors. Thus, a study in Thailand found that MA users were introduced to MA by individuals close to them (Sherman et al., 2008). These findings confirm that the environment or context, including family household, is a significant predictor of early MA use. The attitude of favoring MA use may be mediated by an individual thinking that substance use is normal based on their experience of someone in the family using the substance. Antisocial personality disorder may also be hereditary (Ferguson, 2010; Gunter et al., 2010). Individuals with certain personality disorders, especially antisocial and borderline personality disorders, are more prone to substance use disorders (Cohen et al., 2007; Embry et al., 2009). Common characteristics such as impulsivity were observed among individuals with antisocial personality disorder and substance use disorders, and may be used to explain the study results.

Several limitations of the present study should be discussed. First, the major limits of our data were based on a clinical group of inpatients hospitalized for MA use; therefore, our data were not designed to study other substance use in order to predict MA use/dependence in the general population. In addition, the results from this study could not be used to draw conclusions beyond observed associations that are unlikely to be causal. Although a range of MA use severity was observed in our cohort (i.e., 26% was exposed but not dependent on MA), application and generalization, if any, to other populations should be limited to only people who present for MA treatment with hospitalization. Future studies should examine MA use and dependence in the general population in order to study other substance use related to MA use. Second, we examined only MA cohorts; therefore, further studies should examine cohorts with use of other substances, including cannabis or inhalants, to confirm results regarding age at onset of those substances. Third, because our data were based on retrospective interviews, data involving age at onset of use of the substances may be subject to recall bias. Last, the effects of nicotine, alcohol, inhalants, and cannabis use on the survival time were not examined separately. In conclusion, although the age of onset for MA was later than that for other substances, a substantial proportion of people in the sample (36%) had initiated MA use prior to smoking tobacco or drinking alcohol, and there was no difference between the age of onset for MA and cannabis use. Social and legal policy may partly contribute to this result.

5. Conclusion

We suggest that treatment and prevention strategies should target the use of legal and other illegal substances in parallel with that of MA. Our results may be used for public warning/education that substance use, even substances widely known as legal or soft drugs, may be associated with increased risk or vulnerability (i.e., shortening the course) for MA

dependence at least in a selected population in a treatment setting. Overall, our study provides new knowledge on the pattern of substance use initiation that may be useful for public education and the development of new preventive strategies in drug use policy. Nevertheless, further studies in individuals with non-problem MA use, not included in the current study, are warranted.

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Figure.

Comparison of the median survival time from onset of methamphetamine (MA) initiation to MA dependence between those who used other substances (e.g., alcohol, nicotine, cannabis, inhalants) later or concurrent to MA onset (MA>OTH) and those who used other substances prior to MA onset (OTH>MA) (n = 729) by Kaplan-Meier survival analysis and log-rank test (p = 0.02).

Age of first use of methamphetamine and other substance use, age of dependence, and pairwise comparison of the age onset of the first use of each substance and methamphetamine

Table 1

	Age of first use Mean $\pm$ S.D. (years)		Z	P-values	Age of dependence Mean $\pm$ S.D. (years)	
	MA	Other substance				
MA (N = 991)	18.9 $\pm$ 5.6	-	-	-	21.4 $\pm$ 6.2 (n = 729)	
Nicotine (n = 956)	18.5 $\pm$ 5.5	16.2 $\pm$ 4.2	-14.85	< 0.001 **	21.3 $\pm$ 5.5 (n = 554)	
Alcohol (n = 955)	18.6 $\pm$ 5.6	17.0 $\pm$ 4.2	-9.74	< 0.001 **	22.8 $\pm$ 6.4 (n = 230)	
Inhalants ^a (n = 111)	18.2 $\pm$ 5.4	15.4 $\pm$ 3.5	-5.07	< 0.001 **	15.4 $\pm$ 3.5 (n = 55)	
Cannabis ^b (n = 180)	18.0 $\pm$ 6.3	17.1 $\pm$ 3.5	-0.86	0.388	17.4 $\pm$ 8.2 (n = 54)	

MA = methamphetamine

SD = standard deviation

* p < 0.001, Wilcoxon signed-rank test

^a Individuals with more than 10 episodes of inhalant use

^b Individuals with more than 10 episodes of cannabis use

Table 2

Demographic, diagnostic, and environmental differences between the OTH>MA versus MA>OTH groups and early-onset versus late-onset MA use

	Sequence of substance use				Onset of MA use			
	OTH>MA (n=633)		MA>OTH (n=358)		Early (n=295)		Late (n=696)	
	n	%	n	%	n	%	n	%
Age (years)								
28	294	46.5	119	33.2	59	20.0	354	50.9
23-27	130	20.3	114	31.8	95	32.2	149	21.4
18-22	209	33.0	125	39.9	141	47.8	193	27.7
Age of MA onset (years)	19.9	(6.1)	16.2	(3.4)	-	-	-	-
Mean (SD)								
Sex: Female	272	42.9	198	55.3	131	44.4	339	48.7
History of MA in family	50	7.9	43	12.0	51	17.3	42	6.0
Traumatic event exposure	172	27.2	75	20.9	76	25.8	171	24.6
Antisocial personality	99	15.6	56	15.6	63	21.4	92	13.2
Alcohol dependence	169	26.7	62	17.3	73	24.7	158	22.7
Nicotine dependence	376	59.4	177	49.4	188	63.7	365	52.4
Cannabis dependence	42	6.6	12	3.3	24	8.1	30	4.3
MA = methamphetamine								

MA>OTH = using other substances (e.g., alcohol, nicotine, cannabis, inhalants) later or concurrent to MA-onset

OTH>MA = using other substance prior to MA onset

Early onset = age onset of MA use 15 years old

Late onset = age onset of MA use > 15 years old

SD = standard deviation

*
p < 0.05,

**
p < 0.01,

p < 0.001, two-tailed χ^2 test.

Log transformation, 1989 = 11.9, $p < 0.001$, two-tailed unpaired t-test.

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Table 3

Results of logistic regression analyses for methamphetamine use as first substance and for early-onset methamphetamine use

	B	SE	Wald	df	Adjusted ORs	P-values	95% CI	
							Lower	Upper
Explanatory variables for MA>OTH ^a								
Female	0.61	0.14	19.35	1	1.84	<0.001	1.40	2.42
Nicotine dependence	-0.45	0.14	10.69	1	0.64	0.001	0.49	0.84
Traumatic event	-0.40	0.16	6.07	1	0.67	0.014	0.48	0.92
Constant	-0.41	0.15	7.42	1	0.66	0.006		
Explanatory variables for early MA onset ^b								
Nicotine dependence	0.44	0.15	9.24	1	1.55	0.002	1.17	2.07
Family history of MA	1.16	0.22	26.93	1	3.18	<0.001	2.05	4.92
Constant	-1.24	0.12	115.85	1	0.29	<0.001		

N=991, missing data were not observed.

MA = methamphetamine, ORs = odds ratio, CI = confidence interval, SE = standard error, df = degree of freedom, MA>OTH = use of other substance (e.g., alcohol, nicotine, cannabis, inhalants) later or concurrent to MA onset

^aResults were based on a logistic regression model that was controlled for age group; history of methamphetamine use in family and alcohol, nicotine, and cannabis dependence^bResults were based on a logistic regression model that was controlled for age group, cannabis dependence, and antisocial personality