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Clinical features of methamphetamine-induced paranoia and preliminary genetic association with *DBH* −1021C→T in a Thai treatment cohort

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Abstract

Aims—To explore clinical features of methamphetamine-induced paranoia (MIP) and associations between MIP and a genetic polymorphism in dopamine β-hydroxylase (*DBH* −1021C→T).

Design—Retrospective analysis of clinical presentation and genetic association by chi-square test and logistic regression analysis.

Setting—A Thai substance abuse treatment center

Participants—727 Methamphetamine-dependent (MD) individuals

Measures—Clinical: Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA) and the Methamphetamine Experience Questionnaire (MEQ). Genetic: *DBH* −1021C→T.

Findings—Forty percent of individuals (289 of 727) with MD had MIP. Within-binge latency to MIP onset occurred more rapidly in the most recent compared with initial MIP episode (p=0.02), despite unchanging intake (p=0.89). Individuals with MIP were significantly *less* likely to carry lower (TT/CT) compared with higher (CC) activity genotypes (34% vs 43%; χ^2_1=5, p=0.03). *DBH* effects were confirmed (OR=0.7, p=0.04) after controlling for associated clinical variables (MD severity, OR=3.4, p<0.001; antisocial personality disorder, OR=2.2, p<0.001; alcohol dependence, OR=1.4, p=0.05; and nicotine dependence, OR=1.4, p=0.06). TT/CT carriers were

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more likely to initiate cigarette smoking (OR=3.9, p=0.003) and probably *less* likely to be dependent on alcohol (OR=0.6, p=0.05).

Conclusions—Among methamphetamine-dependent individuals, paranoia appears to occur increasingly rapidly in the course of a session of methamphetamine use. Severity of methamphetamine dependence and antisocial personality disorder predicts methamphetamine-induced paranoia. The genetic polymorphism in dopamine β-hydroxylase is associated with methamphetamine-induced paranoia and influences smoking initiation.

Keywords

methamphetamine; paranoia; psychosis; smoking; DBH; gene

Introduction

In 2011, an estimated 14–53 million people used amphetamine-type stimulants (ATS) globally, making ATS the second most popular illicit substances in the world after cannabis (1). In Thailand, methamphetamine (MA) or “yaba” is the most prevalent ATS by far (2), and recent reports show annual prevalence rates of >1% among 15–64 year olds (rates, higher than worldwide averages; 0.7%) (1). Given the high prevalence, Thailand is a potentially informative location for studying both the environmental and genetic risk factors for ATS use and its complications (3–5) in humans.

Paranoia, defined here operationally as an irrational distrust or fear of others despite the absence of realistic potential for harm (6), occurs in 46–76% of experienced MA users (7–13). It is the primary symptom associated with MA-psychosis (14–17), and it can extend beyond states of acute intoxication, lasting anywhere from several days to months, and may even persist in some cases (13, 18, 19). Previous studies suggest that there is a heritable component (13, 20), and several genetic markers have been suggested to be associated with the trait (13, 21–23). Most commonly, methamphetamine-induced paranoia (MIP) is a short-lived phenotype that is expressed during MA intoxication and resembles other forms of stimulant-induced suspiciousness (e.g., cocaine-induced paranoia or CIP) (11, 24, 25).

Previously, we reported a genetic association between CIP and a functional polymorphism in the dopamine β-hydroxylase (DβH) gene (26). To our knowledge, genetic risk factors for MIP in humans have not been previously reported. We therefore pursued a candidate gene study of MIP in a large cohort rigorously characterized for clinical features and other environmental risk factors associated with the trait. Finding genetic risk factors for MIP, a MA-induced psychosis spectrum trait, may shed light on potential vulnerability or protective factors for other psychotic illnesses.

DβH is the sole enzyme responsible for converting dopamine (DA) to norepinephrine (NE) in humans. Measures of DβH enzyme activity and/or the genetic markers linked to its activity have been previously reported to be associated with substance- and nonsubstance-related psychosis (27–35) and substance (i.e., alcohol, nicotine) use or dependence (35–38). Prior work has demonstrated that 50% of the variance in plasma enzyme activity is explained by a putative functional polymorphism (*−1021 C→T*) in the DβH gene (39).

Since its identification, this single nucleotide polymorphism (SNP) has been found to be associated with a number of neuropsychological phenotypes, including those related to substance use traits. For example, the low-activity T allele was associated with impulsive personality styles (40), fewer cigarettes smoked per day (41), and CIP in a human laboratory paradigm of cocaine self-administration (26). Such findings motivated our exploration of clinical and genetic risk factors for MIP in a reasonably large cohort (N=727).

Methods

Subjects

Thai-speaking MA users age 18 years or above were recruited from Thanyarak Institute, a substance dependence treatment center in Central Thailand where they were hospitalized for four-months of MA rehabilitation treatment between 2007 and 2011. The study ran as part of an ongoing genetic study of MIP which included data from a smaller, overlapping studies of MIP risk factors (N=96) (7) and inhalant use (n = 456) in MA users (42). Exclusion criteria were similar across studies, including 1) lifetime use of MA < 11 instances; 2) history of primary psychotic disorders; 3) brain disease(s) (i.e., epilepsy, stroke, brain trauma). In addition, only subjects with MA dependence (N = 727 out of 990 MA users) were included in the current study. All subjects underwent voluntary written informed consent prior to their research participation and were compensated (500 baht, or roughly US $15), per IRB-approved protocol.

Diagnostic assessments were performed during each subject's rehabilitation period using a Thai version of the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA) (43, 44). Additional information on clinical manifestations of MA use, including MIP, was obtained retrospectively using the Thai language version of the Methamphetamine Experience Questionnaire (MEQ) (7). Both instruments were implemented as computerized versions (see below) and conducted by interviewers (all with bachelors degrees in psychology or higher) certified for their use based on a standard training protocol (ten SSADDA training interviews followed by two qualifying/examination interviews). Interviews were subjected to a rigorous quality control process, including editing and cross-editing by interviewers and review by the principal investigator (RK). The study was approved by The Faculty of Medicine, Chulalongkorn University Institutional Review Board (Med Chula IRB), The Ethical Review Committee for Research in Human Subjects, Thailand Ministry of Public Health, and the Research Committee, Thanyarak Institute on Drug Abuse.

Assessments

The SSADDA is a comprehensive semi-structured diagnostic interview used in genetic studies of substance dependence and related phenotypes (44). Our group developed a Thai version of the SSADDA, which was translated, back-translated, and validated in genetic studies of opioid dependence in Northern Thailand, where it was shown to have both high inter-instrument validity ($\kappa = 0.97$) and inter-rater reliability ($\kappa = 0.97$) (43). Demographic, diagnostic (i.e., antisocial personality disorder or ASPD), attention deficit hyperactivity disorder or ADHD, anxiety disorders) and substance-use data (i.e., onset, duration, amount

and frequency during period of heaviest use) are available in sections on tobacco, alcohol, MA (cocaine in the English version), opioids, and other substances (i.e., cannabis, solvents, other stimulants). The diagnosis of substance dependence is based on the Diagnostic Statistical Manual for Mental Disorder 4th revision (DSM-IV). In the present study, we used number of DSM-IV criteria met for MA dependence (range between 3–7 criteria) to determine severity of MA dependence (MD).

In the current study, we evaluated the concurrent validity of a SSADDA diagnosis of MA dependence with respect to that established by the Mini International Neuropsychiatric Inventory (M.I.N.I) - lifetime Thai version (43) in 79 MA users by kappa statistics. We also assessed the instrument's inter-rater reliability, examining the agreement between interviewers according to the number of DSM-IV criteria met for MA dependence (intraclass correlation) and a diagnosis of MIP (kappa statistic).

The Thai MEQ (7) was adapted from the Yale Cocaine Experience Questionnaire (Yale CEQ), substituting "yaba" (the common term for MA) for "cocaine" (6), and was used to explore paranoid experiences during MA use (7). The presence or absence of MIP was evaluated based on a specific probing algorithm beginning with a thorough description of the trait, followed by the two criteria questions ("Have you ever had a paranoid experience?" and "Have you ever had a paranoid experience while using yaba?"). Affirmative responses to both questions define the MIP phenotype, which has been shown previously to have high reliability across instruments ($\kappa = 0.87$) (Thai SSADDA and Thai MEQ) (7). Clinical features of MIP (age of onset, accompanying psychotic symptoms, behavioral response to MIP experience) were obtained from the MEQ by retrospective interview, as were four additional variables relating to the onset and progression of the trait (i.e., amount of MA use, latency to MIP within a binge, latency to staying awake, and MIP duration).

Genotyping

Genotyping was done at the Center of Excellence in Molecular Genetics of Cancer and Human Diseases, Department of Anatomy, Faculty of Medicine, Chulalongkorn University. DNA was extracted from 10 milliliters of whole blood using a ZR Genomic DNA I kit™ (Silica Bead Format) (Zymo Research, Irving, CA). A restriction fragment length polymorphism (RFLP) method was used to obtain genotypic data at *DBH* −1021C→T (rs1611115) for each subject, as described elsewhere (45). In brief, *DBH* −1021C→T was amplified by polymerase chain reaction (PCR) method. The PCR product was digested using *Hha*I. The digested product was visualized using an 8% acrylamide gel, size fractionated to identify the T and C alleles. About 10% of assays in all genotyping plates were repeated for quality control. Of 727 DNA samples, *DBH* data for 55 (7.6%) could not be obtained. Genotypic data were double-scored by two independent researchers. Deviation from Hardy Weinberg equilibrium expectations was assessed in the total cohort and diagnostic subgroups.

Data analysis

Clinical characteristics of MIP were explored both through descriptive statistics and visual inspection of each variable's underlying distribution within the populations. Non-normally

distributed continuous variables were categorized prior to analyses (age, MA pills per day, MA use duration). MA use, and characteristics of MIP (including onset and course), were compared among MA-dependent individuals with MIP using a McNemar test. In addition, demographic, diagnostic, and MA use variables were compared between MA-dependent individuals with and without MIP by using two-tailed chi-square or unpaired t-test and were entered in the binary logistic regression analysis of MIP in an exploratory manner to identify clinical variables possibly associated with the risk for MIP.

In genetic association analyses, subjects were excluded if three or four grandparents were of non-Thai (e.g., Chinese) ancestry. MIP and clinical features of MIP were first explored according to genotypic group (TT vs. CT vs. CC) by two-tailed, 2x3 heterogeneity chi-square test. C- and T – allele frequency were compared by two-tailed chi-square test. TT and CT were also binned for the purpose of a third statistical analysis. Additional variables were then incorporated in the genetic logistic regression analyses for MIP. Clinical risk factors for MIP identified by the logistic regression analysis described above were then tested for their interactions with the gene on MIP. Specifically, interaction between the binary genotypic variable (CC vs TT/CT) and a clinical risk factor was entered first into the binary logistic regression analysis of MIP, controlling subsequently by the remaining previously identified environmental risk factors. Finally, genetic associations of *DBH* with identified clinical risk factors for MIP and available related variables with the risk were explored by chi-square tests and logistic regression analyses after controlling for MIP status, demographic, diagnostic and MA-use variables.

Results

Inter-rater reliability and concurrent validity of MA dependence and MIP using Thai SSADDA

Diagnostic assessments of MD ascertained via the SSADDA and MINI were in substantial agreement (κ=0.69; MD prevalence = 78%; n = 79). Inter-rater reliability for number of DSM-IV MD criteria met on the SSADDA was high (ICC = 0.81; means = 5.2 ±2.0 vs 5.0 ± 2.0, n = 79). The Thai version of the SSADDA also showed moderate inter-rater reliability for the diagnosis of MIP (κ = 0.46; MIP prevalence = 16%; n = 79).

Clinical features of MIP using the Thai MEQ

Of 990 MA users, 727 (73.4%) met DSM-IV criteria for MD of whom 289 (39.8%) had MIP. In contrast, MIP occurred in 19 (7.2%) of 263 non-dependent MA users. Age of paranoia onset, latency of symptom onset (time between first MA use and first paranoid symptoms), clinical features of MIP and MIP behaviors, and co-occurring psychotic symptoms are shown in Table 1. MIP was endorsed as an aversive feeling and rated as significantly distressing. In general, paranoia occurred when using MA while alone by oneself, followed by using with others; when using MA in a familiar place, followed by using in new place and no difference in person or place respectively, at the time when MIP typically occurred. The majority smoked MA and used MA daily or almost daily.

After an initial paranoid episode, MIP was frequently associated with continued use. A majority of individuals who experienced MIP more than once reported that their paranoia intensified when using higher doses of MA and stated that their most recent MIP experience was more vivid than or equal to their first experience. Latency to MIP onset within a binge (the interval between the first dose of MA and the beginning of paranoid feelings) was significantly shorter in their most recent, as compared to their initial, MIP episode. However, the amount of MA (pills per day), duration of MIP occurrence, and latency of staying awake at the time of later episodes of MIP did not differ compared to those at initial occurrence (Table 1).

Demographic, diagnostic, and drug-use variables and MIP

Individuals with MIP were younger at first use of MA and reported more severe MA use than those without (Table 2). In addition, individuals with MIP were more likely to have a comorbid psychiatric diagnosis, including ASPD, social phobia, suicide attempt, pathological gambling, nicotine dependence, and alcohol dependence, than those without, by univariate analyses. With respect to the logistic regression analysis, severity of MA dependence as measured by DSM-IV symptom count was the most significant associated (likely risk) factor for the trait, followed by ASPD, alcohol dependence and nicotine dependence. Fewer episodes of MA use in the past year had a trend association with MIP (Table 2).

Other demographic (age, sex, race, marital status, employment status, and household gross income), diagnostic (PTSD, ADHD, conduct disorder), and drug use (duration, or cessation of MA use) variables did not differ between those with and without MIP (Table 2).

DBH gene variant and MIP

Only Thai subjects were entered into the analysis of genetic association (N = 646), to minimize population stratification. We observed no evidence of deviation from Hardy Weinberg Equilibrium expectations in the entire MA dependent sample (X^2_2= 1.1, p = 0.58) and each subgroup (MIP, n = 261, X^2_2= 0.8, p = 0.67; non-MIP, n = 385, X^2_2= 0.4, p = 0.83).

Among MD individuals, lower T-allele frequency was observed in the MIP as compared to non-MIP group (Table 3). C-homozygotes did not significantly differ in MIP frequency compared to either the hetero- or T-homozygotes, but when the latter two groups were combined for a post-hoc exploratory analysis, the result was nominally significant. None of clinical features of MIP were associated with genotype or allele frequency of the gene (Table 3). Genetic associations with MIP were confirmed by logistic regression analysis (Tables 3 and 4). A significant interaction of gene by severity of MD was observed (Table 4). However, interaction between gene and ASPD or gene and nicotine/alcohol dependence did not predict MIP.

DBH gene variant and identified clinical risk factors for MIP

Clinical risk factors for MIP (e.g., severity of MD, ASPD, nicotine dependence, alcohol dependence) and available clinical data related to the risk factors, including MA use

variables (related to severity of MD), conduct disorder (related to ASPD), nicotine initiation (46) (ever vs never been a regular smoker, e.g., used ≥ 100 cigarettes lifetime; related to nicotine dependence), and alcohol flush syndrome (i.e., flushing after 1–2 drink of alcohol; related to protection from alcohol dependence) were explored for genetic association with *DBH* gene variant. TT/CT genotypes and T-allele were associated with nicotine initiation, non-alcohol dependence and shorter duration of MA use in lifetime (Table 5). However, only a genetic association of *DBH* with nicotine initiation was confirmed by logistic regression analysis (p=0.003). TT/CT genotypes were associated at trend level with protection for alcohol dependence (p=0.05) and prolonged duration of MA-use (p=0.06), from logistic regression analysis.

Discussion

Results of our study point strongly to the importance of severity of MD, comorbid alcohol or nicotine dependence, and ASPD in predicting the onset of MIP. The low-activity T-allele at *DBH* −1021C→T possibly protects from the occurrence of MIP and predicts nicotine initiation. In addition, and consistent with mechanisms of sensitization, MIP occurred more rapidly over the course of MA use in the face of unchanging MA intake. Ours is the largest cohort studied to date to examine such clinical and genetic risk factors for MIP.

DBH is a gene located on chromosome 9q34 spanning 22,982 base pairs. The −1021C→T marker of the *DBH* is located at the 5′ promoter region and previously shown to associate with markers of DβH enzyme activity (and is thus functionally relevant). While a low-activity allele or haplotype of *DBH* was previously found to be associated with paranoia while under the influence of cocaine (26, 28), the high-activity C-allele was nominally associated with MIP in the current study. Although there is a very large preclinical and clinical literature demonstrating similarities across stimulants (e.g., including cocaine and methamphetamine) (47, 48), we cannot rule out the possibility of differences that derive from pharmacological mechanisms (e.g., pure reuptake inhibitor vs. a releaser/reuptake inhibitor, respectively) and/or pharmacokinetics (e.g., relatively shorter vs. longer half-lives) of the drugs (49, 50). For example, the latency to MIP within a binge is much longer than that of CIP (hours for MIP (Table 1) vs. minutes for CIP (6, 51)), suggesting different mechanism of the trait (perhaps oxidative stress and neurotoxicity in MA use (3, 52)) rather than immediate synaptic DA hyperactivity. Although this seems an unlikely explanation, alternatively, methodological limitations of the current work may account for such differences. Further, when corrected for multiple statistical tests, our results are not considered statistically significant, and thus replication in a larger sample is necessary.

The effects of dependence on other substances (e.g., alcohol, nicotine) on MIP are consistent with previous findings (7, 12, 13). In addition, the low-activity T-allele and TT/CT genotypes were associated with cigarette-smoking initiation, while appearing statistically protective towards alcohol dependence and long-term MA use. While such findings are consistent with previous reports on *DBH* and smoking behaviors (37, 41, 46, 53, 54) and alcohol dependence (36, 38), future replication is warranted to confirm these seemingly opposite effects on substance dependence vulnerability.

The effect of severity of MA dependence (DSM symptom count) on MIP is consistent with previous findings (7, 12, 13). While other measures of MA use were also associated with MIP in initial analyses, they did not survive the logistic regression analysis (except for a trend association between MIP and “fewer” episodes of MA use in last year, consistent with the aversive effect of drug-induced paranoia in previous studies) (6, 55). Findings of an interaction between *DBH* and MD severity with respect to the occurrence of MIP are also intriguing, suggesting the importance of gene by environment interactions, as previously suggested.

A majority of MIP individuals reported an increase in the intensity of their paranoia over the course of their use. The more rapid onset of paranoia during use in the face of other unchanging clinical features (latency to sleep, lack of change in MA use), are consistent with mechanisms of sensitization (6, 12, 56). Although MIP duration was usually about 3–4 hours and did not change significantly over the course of MIP, nearly one in five individuals endorsing MIP reported persistence of symptoms even after discontinuing MA and even after other intoxicating effects of the drug (e.g., ‘high’ or euphoria) had waned, raising questions about potential continuities between the trait and more severe versions of MA-psychosis (at least in such subgroups). Interestingly, a majority (68%, 34 out of 50) of the individuals who endorsed a ‘sensitizing’ pattern to their MIP experienced prolonged paranoia (e.g., MIP lasting longer than the average duration of MIP or ≥ 4 hours).

Several limitations deserve mention. First, the study was performed retrospectively, and clinical features of MIP and its associated variables might be subject of recall bias. In addition, despite our cohort being the largest sample to report on MIP to date, it is still modest in size, and we cannot exclude the possibility that a larger cohort would have substantially changed our findings. The power of the study is 50% based on a MAF for *DBH C->−1021->T* of 18% (57). In addition, the current approach, namely a candidate gene study, carries a number of limitations. Although we based our rationale for examining *DBH* on two prior findings of stimulant- (cocaine-) induced paranoia, this is the first study, to our knowledge, to examine MIP. It remains our long-term interest to employ genome-wide methods to study genetic risk factors for MIP. However, our current sample remains modest in comparison to samples typically required of complex trait genomewide association studies (where case-control cohorts of several thousand or more are typical). In addition, the current study did not employ genetic methods (e.g., structured association or genomic control) to exclude the possibility of Type I error resulting from population stratification artifact. For example, though a relatively homogenous population in comparison to many western populations, and although we took steps to specifically exclude individuals of non-Thai heritage from our genetic association analyses, Thais are known to have two primary ancestral origins, including both Tai and Chinese roots; and there are also individuals of minority Hill Tribe ancestry. In addition, recent analysis of data from genome-wide association studies conducted in the Thai population have indicated that at least four genetically distinct subpopulation clusters may exist, requiring up to 5000 ancestry-informative SNP markers to identify with 99% accuracy (unpublished data, Tongsima 2012). Thus, we view this as a major limitation of the current study, and we believe our finding requires future replication efforts that specifically control for population

stratification before the current genetic association can be viewed as anything other than preliminary. Finally, we did not apply Bonferroni-corrected p-values for the multiple comparisons conducted, and for these reasons as well, they must be regarded as preliminary.

In conclusion, our results show variation in the clinical features of MIP and support its sensitizing nature over the course of MA dependence. Our preliminary findings also raise the possibility of a genetic risk factor for the trait, but require verification. Future studies of much larger case:control cohorts employing more rigorous genetic methods will ultimately be required to more definitively identify genetic risk factors for the trait.

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References

1. UNODC. World Drug Report 2013: United Nations publication. Report No.: Sales No. E.13.XI.6
2. Office of the Narcotics Control Board. Statistics on drug cases throughout the country January 1 – December 31, 2011. Bangkok: 2012. [updated June 12, 2012]; Available from: http://www.webcitation.org/6LhhJjnTE
3. Carvalho M, Carmo H, Costa VM, Capela JP, Pontes H, Remiao F, et al. Toxicity of amphetamines: an update. Arch Toxicol. 2012; 6:6.
4. Kaye S, McKetin R, Duflou J, Darke S. Methamphetamine and cardiovascular pathology: a review of the evidence. Addiction. 2007; 102(8):1204–11. [PubMed: 17565561]
5. Hawks D, Mitcheson M, Ogborne A, Edwards G. Abuse of methylamphetamine. Br Med J. 1969; 2(5659):715–21. [PubMed: 5786759]
6. Satel SL, Southwick SM, Gawin FH. Clinical features of cocaine-induced paranoia. Am J Psychiatry. 1991; 148(4):495–8. [PubMed: 2006696]
7. Kalayasiri R, Mutirangura A, Verachai V, Gelernter J, Malison RT. Risk factors for methamphetamine-induced paranoia and latency of symptom onset in a Thai drug treatment cohort. Asian Biomedicine. 2009; 3(6):635–43.
8. Hall W, Hando J, Darke S, Ross J. Psychological morbidity and route of administration among amphetamine users in Sydney, Australia. Addiction. 1996; 91(1):81–7. [PubMed: 8822016]
9. Sommers I, Baskin D, Baskin-Sommers A. Methamphetamine use among young adults: health and social consequences. Addict Behav. 2006; 31(8):1469–76. [PubMed: 16309848]
10. McKetin R, McLaren J, Lubman DI, Hides L. The prevalence of psychotic symptoms among methamphetamine users. Addiction. 2006; 101(10):1473–8. [PubMed: 16968349]
11. Mahoney JJ 3rd, Kalechstein AD, De La Garza R 2nd, Newton TF. Presence and persistence of psychotic symptoms in cocaine- versus methamphetamine-dependent participants. Am J Addict. 2008; 17(2):83–98. [PubMed: 18393050]

12. Leamon MH, Flower K, Salo RE, Nordahl TE, Kranzler HR, Galloway GP. Methamphetamine and paranoia: the methamphetamine experience questionnaire. Am J Addict. 2010; 19(2):155–68. [PubMed: 20163388]
13. Grant KM, LeVan TD, Wells SM, Li M, Stoltenberg SF, Gendelman HE, et al. Methamphetamine-associated psychosis. J Neuroimmune Pharmacol. 2012; 7(1):113–39. [PubMed: 21728034]
14. Sato M, Numachi Y, Hamamura T. Relapse of paranoid psychotic state in methamphetamine model of schizophrenia. Schizophr Bull. 1992; 18(1):115–22. [PubMed: 1553491]
15. Connell, PH. Amphetamine psychosis. London: Oxford University Press; 1958.
16. Srisurapanont M, Ali R, Marsden J, Sunga A, Wada K, Monteiro M. Psychotic symptoms in methamphetamine psychotic in-patients. Int J Neuropsychopharmacol. 2003; 6(4):347–52. [PubMed: 14604449]
17. Chen CK, Lin SK, Sham PC, Ball D, Loh EW, Hsiao CC, et al. Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. Psychol Med. 2003; 33(8): 1407–14. [PubMed: 14672249]
18. Kittirattanapaiboon P, Mahatnirunkul S, Booncharoen H, Thummawomg P, Dumrongchai U, Chutha W. Long-term outcomes in methamphetamine psychosis patients after first hospitalisation. Drug Alcohol Rev. 2010; 29(4):456–61. [PubMed: 20636664]
19. Tucker P. Substance misuse and early psychosis. Australas Psychiatry. 2009; 17(4):291–4. 20090708 DCOM- 20090916. [PubMed: 19301164]
20. Chen CK, Lin SK, Sham PC, Ball D, Loh el W, Murray RM. Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. Am J Med Genet B Neuropsychiatr Genet. 2005; 5(1):87–91. [PubMed: 15892150]
21. Bousman CA, Glatt SJ, Everall IP, Tsuang MT. Genetic association studies of methamphetamine use disorders: A systematic review and synthesis. Am J Med Genet B Neuropsychiatr Genet. 2009; 5(8):1025–49. [PubMed: 19219857]
22. Kotaka T, Ujike H, Okahisa Y, Takaki M, Nakata K, Kodama M, et al. G72 gene is associated with susceptibility to methamphetamine psychosis. Prog Neuropsychopharmacol Biol Psychiatry. 2009; 33(6):1046–9. [PubMed: 19482054]
23. Kishimoto M, Ujike H, Motohashi Y, Tanaka Y, Okahisa Y, Kotaka T, et al. The dysbindin gene (DTNBP1) is associated with methamphetamine psychosis. Biol Psychiatry. 2008; 63(2):191–6. 20071231 DCOM- 20080227. [PubMed: 17555717]
24. Mahoney JJI, Hawkins RY, De La Garza R, Kalechstein AD, Newton TF. Relationship between gender and psychotic symptoms in cocaine-dependent and methamphetamine-dependent participants. Gend Med. 2010; 7(5):414–21. [PubMed: 21056868]
25. Ellison G. Stimulant-induced psychosis, the dopamine theory of schizophrenia, and the habenula. Brain Res Brain Res Rev. 1994; 19(2):223–39. [PubMed: 7914793]
26. Kalayasiri R, Sughondhabirom A, Gueorguieva R, Coric V, Lynch WJ, Lappalainen J, et al. Dopamine beta-hydroxylase gene (DbetaH) −1021C-->T influences self-reported paranoia during cocaine self-administration. Biol Psychiatry. 2007; 61(11):1310–3. [PubMed: 17157269]
27. Wood JG, Joyce PR, Miller AL, Mulder RT, Kennedy MA. A polymorphism in the dopamine beta-hydroxylase gene is associated with “paranoid ideation” in patients with major depression. Biol Psychiatry. 2002; 51(5):365–9. [PubMed: 11904130]
28. Cubells JF, Kranzler HR, McCance-Katz E, Anderson GM, Malison RT, Price LH, et al. A haplotype at the DBH locus, associated with low plasma dopamine beta-hydroxylase activity, also associates with cocaine-induced paranoia. Mol Psychiatry. 2000; 5(1):56–63. [PubMed: 10673769]
29. Meyers BS, Alexopoulos GS, Kakuma T, Tirumalasetti F, Gabriele M, Alpert S, et al. Decreased dopamine beta-hydroxylase activity in unipolar geriatric delusional depression. Biol Psychiatry. 1999; 45(4):448–52. [PubMed: 10071716]
30. Hamner MB, Gold PB. Plasma dopamine beta-hydroxylase activity in psychotic and non-psychotic post-traumatic stress disorder. Psychiatry Res. 1998; 77(3):175–81. [PubMed: 9707300]
31. Meltzer HY, Tong C, Luchins DJ. Serum dopamine-beta-hydroxylase activity and lateral ventricular size in affective disorders and schizophrenia. Biol Psychiatry. 1984; 19(10):1395–402. [PubMed: 6335052]

32. Major LF, Lerner P, Ballenger JC, Brown GL, Goodwin FK, Lovenberg W. Dopamine-beta-hydroxylase in the cerebrospinal fluid: relationship to disulfiram-induced psychosis. Biol Psychiatry. 1979; 14(2):337–44. [PubMed: 476222]
33. Belmaker RH, Hattab J, Ebstein RP. Plasma dopamine-beta-hydroxylase in childhood psychosis. J Autism Child Schizophr. 1978; 8(3):293–8. [PubMed: 211113]
34. Meltzer HY, Cho HW, Carroll BJ, Russo P. Serum dopamine-beta-hydroxylase activity in the affective psychoses and schizophrenia. Decreased activity in unipolar psychotically depressed patients. Arch Gen Psychiatry. 1976; 33(5):585–91. [PubMed: 1267575]
35. Cubells JF, Zabetian CP. Human genetics of plasma dopamine beta-hydroxylase activity: applications to research in psychiatry and neurology. Psychopharmacology (Berl). 2004; 174(4): 463–76. [PubMed: 15088079]
36. Preuss UW, Wurst FM, Ridinger M, Rujescu D, Fehr C, Koller G, et al. Association of functional DBH genetic variants with alcohol dependence risk and related depression and suicide attempt phenotypes: Results from a large multicenter association study. Drug Alcohol Depend. 2013; 133(2):459–67. [PubMed: 23906995]
37. Ella E, Sato N, Nishizawa D, Kageyama S, Yamada H, Kurabe N, et al. Association between dopamine beta hydroxylase rs5320 polymorphism and smoking behaviour in elderly Japanese. J Hum Genet. 2012; 57(6):385–90. [PubMed: 22513716]
38. Kohnke MD, Kolb W, Kohnke AM, Lutz U, Schick S, Batra A. DBH*444G/A polymorphism of the dopamine-beta-hydroxylase gene is associated with alcoholism but not with severe alcohol withdrawal symptoms. J Neural Transm. 2006; 113(7):869–76. [PubMed: 16252068]
39. Zabetian CP, Anderson GM, Buxbaum SG, Elston RC, Ichinose H, Nagatsu T, et al. A quantitative-trait analysis of human plasma-dopamine beta-hydroxylase activity: evidence for a major functional polymorphism at the DBH locus. Am J Hum Genet. 2001; 68(2):515–22. [PubMed: 11170900]
40. Hess C, Reif A, Strobel A, Boreatti-Hummer A, Heine M, Lesch KP, et al. A functional dopamine-beta-hydroxylase gene promoter polymorphism is associated with impulsive personality styles, but not with affective disorders. J Neural Transm. 2009; 116(2):121–30. [PubMed: 18982239]
41. Freire MT, Marques FZ, Hutz MH, Bau CH. Polymorphisms in the DBH and DRD2 gene regions and smoking behavior. Eur Arch Psychiatry Clin Neurosci. 2006; 256(2):93–7. [PubMed: 16032443]
42. Intharachuti W, Ittiwut R, Listman J, Verachai V, Mutirangura A, Malison RT, et al. Polymorphism of COMT Val158Met is associated with inhalant use and dependence: a Thai substance dependence treatment cohort. Asian Biomedicine. 2012; 6(4):549–56.
43. Malison RT, Kalayasiri R, Sanichwankul K, Sughondhabirom A, Mutirangura A, Pittman B, et al. Inter-rater reliability and concurrent validity of DSM-IV opioid dependence in a Hmong isolate using the Thai version of the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA). Addict Behav. 2011; 36(1–2):156–60. [PubMed: 20888699]
44. Pierucci-Lagha A, Gelernter J, Chan G, Arias A, Cubells JF, Farrer L, et al. Reliability of DSM-IV diagnostic criteria using the semi-structured assessment for drug dependence and alcoholism (SSADDA). Drug Alcohol Depend. 2007; 91(1):85–90. [PubMed: 17590536]
45. Zabetian CP, Buxbaum SG, Elston RC, Kohnke MD, Anderson GM, Gelernter J, et al. The structure of linkage disequilibrium at the DBH locus strongly influences the magnitude of association between diallelic markers and plasma dopamine beta-hydroxylase activity. Am J Hum Genet. 2003; 72(6):1389–400. [PubMed: 12730829]
46. Tobacco and Genetics Consortium. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. Nat Genet. 2010; 42(5):441–7. [PubMed: 20418890]
47. Ciccarone D. Stimulant abuse: pharmacology, cocaine, methamphetamine, treatment, attempts at pharmacotherapy. Prim Care. 2011; 38(1):41–58. [PubMed: 21356420]
48. Zhang Y, Loonam TM, Noailles PA, Angulo JA. Comparison of cocaine- and methamphetamine-evoked dopamine and glutamate overflow in somatodendritic and terminal field regions of the rat brain during acute, chronic, and early withdrawal conditions. Ann N Y Acad Sci. 2001; 937:93–120. [PubMed: 11458542]

49. Fowler JS, Volkow ND, Logan J, Alexoff D, Telang F, Wang GJ, et al. Fast uptake and long-lasting binding of methamphetamine in the human brain: comparison with cocaine. Neuroimage. 2008; 43(4):756–63. [PubMed: 18708148]
50. Newton TF, De La Garza RI, Kalechstein AD, Nestor L. Cocaine and methamphetamine produce different patterns of subjective and cardiovascular effects. Pharmacol Biochem Behav. 2005; 82(1):90–7. [PubMed: 16112720]
51. Kalayasiri R, Sughondhabirom A, Gueorguieva R, Coric V, Lynch WJ, Morgan PT, et al. Self-reported paranoia during laboratory “binge” cocaine self-administration in humans. Pharmacol Biochem Behav. 2006; 83(2):249–56. [PubMed: 16549106]
52. Seger D. Cocaine, metamfetamine, and MDMA abuse: the role and clinical importance of neuroadaptation. Clin Toxicol (Phila). 2010; 48(7):695–708. [PubMed: 20849328]
53. McKinney EF, Walton RT, Yudkin P, Fuller A, Haldar NA, Mant D, et al. Association between polymorphisms in dopamine metabolic enzymes and tobacco consumption in smokers. Pharmacogenetics. 2000; 10(6):483–91. [PubMed: 10975602]
54. Siedlinski M, Cho MH, Bakke P, Gulsvik A, Lomas DA, Anderson W, et al. Genome-wide association study of smoking behaviours in patients with COPD. Thorax. 2011; 66(10):894–902. [PubMed: 21685187]
55. Kalayasiri R, Kranzler HR, Weiss R, Brady K, Gueorguieva R, Panhuysen C, et al. Risk factors for cocaine-induced paranoia in cocaine-dependent sibling pairs. Drug Alcohol Depend. 2006; 84(1): 77–84. [PubMed: 16413147]
56. Sato M, Chen CC, Akiyama K, Otsuki S. Acute exacerbation of paranoid psychotic state after long-term abstinence in patients with previous methamphetamine psychosis. Biol Psychiatry. 1983; 18(4):429–40. [PubMed: 6860719]
57. Gauderman, WJ.; Morrison, JM. QUANTO 1.1: A computer program for power and sample size calculations for genetic-epidemiology studies. 2006. Available from: http://hydra.usc.edu/gxe

Table 1

Clinical features, behaviors and co-occurring psychotic symptoms associated with MIP in MA dependent individuals.

	MIP (N = 289)	%
Clinical features of MIP		
Age of MIP onset (median; years) (mean ± SD = 21.6 ± 5.7; min, max = 12, 49)	20	-
Latency of MIP onset (median; years) (mean ± SD = 3.9 ± 3.8; min, max = 0, 18)	3	-
Paranoia at the time of first MA use	22	7.6
MIP occurred once in lifetime	31	10.7
Subsequent paranoia without MA use	24	8.3
Persistence MIP beyond intoxication	50	17.3
MIP frequently associated with continued MA use (median) [b, c] (mean ± SD = 3.2 ± 1.3)	3.0	-
Environmental variables when experiencing MIP		
MA use with or without others [d]		
Alone by oneself	154	53.3
With others	52	18.0
No difference	48	16.6
MA use in familiar or new place [d]		
Familiar place	120	41.5
New place	93	32.2
No difference	43	14.9
Route of MA use		
Smoke	284	98.3
Oral	5	1.7
MA use daily or almost daily	240	83.1
MIP intensified when using higher doses of MA [c]	164	63.6
MIP behaviors and co-occurring symptoms		
Feeling distressed from MIP (median) [a] (mean ± SD = 3.2 ± 1.3)	3.0	-
Response when having MIP		
Hiding	217	75.1
Obtain weapon	78	27.0
Call for help	24	8.3
Attack others	23	8.0
Other psychotic symptoms		
Auditory hallucination	188	65.1
Visual hallucination	81	28.0
Tactile hallucination	34	11.8
Olfactory hallucination	13	4.5
Progression of MIP		
Vividness of last MIP compared to first experience [c, d]		
More vivid	97	37.6

	MIP (N = 289)	%
Clinical features of MIP		
Less vivid	75	29.1
Equal	74	28.7
Latency to MIP onset within a binge [c] (median; hours)		
At MIP onset	11	p=0.02*
At most recent MIP	6	
Duration of MIP [c] (median; hours)		
At MIP onset	4	p=0.66
At later episodes of MIP	3	
Amount of MA use (median; pills per day) [c]		
At MIP onset	5	p=0.89
At later episodes of MIP	5	
Latency of staying awake (median; hours) [c]		
At MIP onset	48	p=0.16
At later episodes of MIP	36	

MIP = methamphetamine- induced paranoia, MA = methamphetamine

[a] 0 = not distressing at all, 5 = intolerable

[b] 0 = never, 5 = always

[c] n = 258

[d] the rest of the group did not know the difference

* $p < 0.05$, McNemar test

Table 2

Methamphetamine (MA) use variables, demographics and diagnoses in individuals with (MIP) and without (non-MIP) paranoia.

	MIP (n = 289)		Non-MIP (n = 438)		Univariate analyses		Multivariate analysis				
	n	%	n	%	χ^2, df	P values	Wald	Adjusted ORs	95% CI		P values
									Lower	Upper	
MA use variables											
MA use duration											
≥ 6 years	182	63.0	272	62.2	0, 1	0.84	1.0	0.8	0.5	1.3	0.30
0 – 5 years	107	37.0	165	37.8							
Daily MA pills during period of heaviest use											
≥ 5	172	59.5	218	49.8	7, 1	0.01**	0.2	1.1	0.7	1.7	0.68
1 – 4	117	40.5	220	50.2							
Daily spent for MA during period of heaviest use											
≥ 1000 baht	147	51.0	185	42.7	5, 1	0.03*	0.04	1.04	0.7	1.6	0.85
< 1000 baht	141	49.0	248	57.3							
MA days per month during period of heaviest use											
21 – 30	197	68.2	262	59.8	5, 1	0.02*	0.3	1.1	0.8	1.6	0.57
1 –20	92	31.8	176	40.2							
Episodes of MA use in lifetime											
≥ 1001	232	80.6	322	74.2	4, 1	0.05*	0.5	1.2	0.7	1.9	0.49
11 – 1000	56	19.4	112	25.8							
Episodes of MA use in last year											
≥ 151	201	70.3	297	70.4	0, 1	0.98	3.8	0.7	0.4	1.0	0.05
0 – 150	85	29.7	125	29.6							
MA dependence severity (DSM-IV symptom count)											
5 – 7 boxes	265	91.7	316	72.1	42, 1	<0.001***	19	3.2	1.9	5.5	<0.001 ***
3 – 4 boxes	24	8.3	122	27.9							
MA cessation	236	81.9	360	82.2	0, 1	0.93	1.5	0.7	0.5	1.2	0.22
Age of MA onset (mean (SD); years)	17.7	(4.9)	18.5	(5.7)	$t_{725} = -2.2$	0.03* (log)	1.1	3.1	0.4	25.8	0.30 (log)
Demographics											

	MIP (n = 289)		Non-MIP (n = 438)		Univariate analyses		Multivariate analysis				
	n	%	n	%	χ^2, df	P values	Wald	Adjusted ORs	95% CI		P values
									Lower	Upper	
Age (years)											
≥ 28	116	40.1	184	42.0	1, 2	0.79	0.4	1.1	0.8	1.5	0.54
23–27	73	25.3	113	25.8							
18–22	100	34.6	141	32.2							
Male	142	49.1	199	45.4	1, 1	0.33	0.02	1.0	0.7	1.5	0.90
Race (Thai)	280	96.9	419	95.7	1, 1	0.40	1.2	1.6	0.7	3.9	0.27
Employment	61	21.1	102	23.3	1, 1	0.49	0.3	0.9	0.6	1.4	0.60
HHI (baht / month) [a]											
0–15000	145	50.2	215	49.2	0, 1	0.80	1.9	1.3	0.9	1.8	0.17
≥ 15001	144	49.8	222	50.8							
Marital status											
Never married	215	74.4	321	73.5	0, 2	0.90	0.1	1.0	0.7	1.2	0.71
Not married [b]	41	14.2	61	14.0							
Married	33	11.4	55	12.6							
Diagnoses											
MDE [c]	2	0.7	4	0.9	0, 1	0.75	0.8	0.4	0.1	2.8	0.37
Suicidal attempt	72	25.0	78	17.8	6, 1	0.02*	2.5	1.4	0.9	2.1	0.11
Conduct disorder	28	9.7	28	6.4	3, 1	0.10	1.4	1.4	0.8	2.6	0.24
ASPD [d]	79	27.3	59	13.5	22, 1	<0.001***	6.0	1.8	1.1	2.7	0.01*
ADHD [e]	3	1.0	2	0.5	1, 1	0.35	0.1	1.5	0.1	27	0.79
PTSD [f]	1	0.3	2	0.5	0, 1	0.82	0.7	0.3	0.03	4.5	0.41
Social phobia	12	4.2	5	1.1	7, 1	0.009**	1.2	1.8	0.6	5.6	0.28
Agoraphobia	1	0.3	1	0.2	0, 1	0.77	0.1	0.7	0.03	16	0.82
Pathological gambling	117	40.5	126	28.8	11, 1	0.001**	0.9	1.2	0.8	1.7	0.35
Other substances											
Nicotine dependence	218	75.4	261	59.6	19, 1	<0.001***	4.7	1.5	1.04	2.2	0.03*
Alcohol dependence	108	37.4	95	21.7	21, 1	<0.001***	6	1.6	1.1	2.4	0.01*

	MIP (n = 289)		Non-MIP (n = 438)		Univariate analyses		Multivariate analysis				
	n	%	n	%	χ^2, df	P values	Wald	Adjusted ORs	95% CI		P values
									Lower	Upper	
Illicit drug use (≥100 times)											
Opioid	18	6.2	21	4.8	1, 1	0.40	0.1	1.1	0.5	2.5	0.74
Cannabis	45	15.6	51	11.6	2, 1	0.13	0.2	1.1	0.7	1.9	0.63
Solvent	25	8.7	37	8.4	0, 1	0.92	2.3	0.6	0.3	1.1	0.13
Ice	43	14.9	59	13.5	0, 1	0.60	0.01	1.0	0.6	1.6	0.91

MIP = MA-induced paranoia

[a]Household gross income,

[b]Widowed, separated, divorced,

[c]Major depressive episode,

[d]Antisocial personality disorder,

[e]Attention deficit hyperactivity disorder,

[f]Posttraumatic stress disorder

***p < 0.001

**p < 0.01

*p < 0.05

Table 3

Genotype and allele frequency of DBH −1021 CT and logistic regression analyses of genetic influences on MIP and MIP clinical features.

	DBH genotypes (N = 646)							*DBH* group					*DBH* alleles					Multivariate analysis [b]			
	TT		CT		CC		P value	TT/CT		CC		P value	T-allele		C-allele		P value	Adjusted ORs	95% CI		P Values
	n	%	n	%	n	%		n	%	n	%		n	%	n	%			Lower	Upper	
MIP vs Non-MIP																					
MIP	9	32.1	64	34.6	188	43.4	0.08	73	34.3	188	43.4	0.03*	82	34.0	440	41.9	0.03*	0.6	0.4	0.9	0.02**
Non-MIP	19	67.9	121	65.4	245	56.6		140	65.7	245	56.6		159	66.0	611	58.1					
Prolonged (≥ 4 hours) MIP (N = 645)																					
Prolonged	3	11.1	33	17.8	93	21.5	0.29	36	17.0	93	21.5	0.18	39	16.3	219	20.8	0.11	0.8	0.5	1.3	0.33
Others [a]	24	88.9	152	82.2	340	78.5		176	83.0	340	78.5		200	83.7	832	79.2					
Early (≤ 18 years) MIP onset																					
Early	5	17.9	25	13.5	65	15.0	0.79	30	14.1	65	15.0	0.75	35	14.5	155	14.7	0.93	0.9	0.5	1.6	0.70
Others [a]	23	82.1	160	86.5	368	85.0		183	85.9	368	85.0		206	85.5	896	85.3					
Early (< 3 years) latency to MIP onset																					
Early	7	25.0	26	14.1	88	20.3	0.13	33	15.5	88	20.3	0.14	40	19.2	202	16.6	0.35	0.6	0.4	1.0	0.06
Others [a]	21	75.0	159	85.9	345	79.7		180	84.5	345	79.7		201	80.8	849	83.4					
Early (<11 hours) latency to MIP onset within a MA binge																					
Early	5	17.9	60	32.4	125	28.9	0.26	65	30.5	125	28.9	0.67	70	29.5	310	29.0	0.89	1.1	0.7	1.6	0.64
Others [a]	23	82.1	125	67.6	308	71.1		148	69.5	308	71.1		171	70.5	741	71.0					
Frequent MIP experience (score > 3 out of 5) with MA use																					
Frequent	5	17.9	21	11.4	67	15.5	0.36	26	12.2	67	15.5	0.27	31	12.9	155	14.7	0.45	0.8	0.4	1.3	0.36
Others [a]	23	82.1	164	88.6	366	84.5		187	87.8	366	84.5		210	87.1	896	85.3					
Accompanying hallucinations																					
Yes	6	21.4	46	24.9	132	30.5	0.26	52	24.4	132	30.5	0.11	58	24.1	310	29.5	0.09	0.7	0.5	1.1	0.13
No	22	78.6	139	75.1	301	69.5		161	75.6	301	69.5		183	75.9	741	70.5					

MA = methamphetamine, DBH = dopamine β-hydroxylase, OR = Odds ratio, 95% CI = 95% confidence interval

[a] Included non-MIP and MIP without the feature.

[b] Influence of DBH gene (TT/CT compared to CC) on MIP and MIP clinical features after demographic, diagnostic and MA-use variables were controlled.

* $X^2_1 = 5$, $p < 0.05$, two tailed.

** $p < 0.05$, logistic regression analysis

Table 4

Logistic regression analysis of genetic influence and gene x environment interaction on MIP compared to non-MIP

	Univariate analyses				P values	Adjusted ORs	95% CI		G x E interaction[b] (P values)
	χ^2, df	P values	Wald	df			Lower	Upper	
DBH gene [a]	4.9, 1	0.03	4	1	0.04 *	0.7	0.5	0.98	-
Severity of MA dependence	42, 1	<0.001	22	1	<0.001**	3.4	2.1	5.7	0.02 *
Antisocial personality	22, 1	<0.001	14	1	<0.001**	2.2	1.5	3.4	0.45
Alcohol dependence	21, 1	<0.001	4	1	0.05	1.4	1.0	2.1	0.99
Nicotine dependence	19, 1	<0.001	4	1	0.06	1.4	1.0	2.1	0.51

MIP = methamphetamine-induced paranoia, MA = methamphetamine, DBH = dopamine β-hydroxylase 95% CI = 95% confidence interval, df = degree of freedom, G x E = gene by environment

[a] TT/CT compared to CC genotype.

[b] After controlling for other clinical variables in the Table.

* $p < 0.05$

** $p < 0.001$

Table 5

Genotype and allele frequency of DBH −1021 CT and logistic regression analyses of genetic influences on identified clinical risk factors for MIP and related variables.

	DBH genotypes (N = 646)							*DBH* group					*DBH* alleles					Multivariate analysis [a]			
	TT		CT		CC		P values	TT/CT		CC		P values	T-allele		C-allele		P values	Adjusted	95% CI		P values
	n	%	n	%	n	%		n	%	n	%		n	%	n	%		ORs	Lower	Upper	
MA use variables																					
MA use ≥ 6 years [b]	16	57.1	101	54.6	286	66.2	0.02*	117	54.9	286	66.2	0.005**	133	55.2	673	64.2	0.01**	0.6	0.3	1.0	0.06
Daily MA ≥ 5 pills [b, c]	14	50.0	102	55.1	232	53.6	0.86	116	54.5	232	53.6	0.83	130	53.9	566	53.9	0.98	1.0	0.6	1.7	0.86
Daily MA ≥ 1000 baht [b, c]	10	35.7	90	48.9	198	46.2	0.41	100	47.2	198	46.2	0.81	110	45.8	486	46.6	0.82	1.0	0.6	1.6	0.93
MA ≥ 21 days per month [b, c]	18	64.3	120	64.9	272	62.8	0.89	138	64.8	272	62.8	0.62	156	64.7	664	63.2	0.65	1.2	0.8	1.7	0.49
Lifetime ≥ 1001 MA episodes [b]	21	75.0	137	74.9	330	76.7	0.87	158	74.9	330	76.7	0.60	179	74.9	797	76.4	0.62	1.1	0.6	1.8	0.86
Last year ≥ 151 MA episodes [b]	17	65.4	128	72.3	295	69.6	0.69	145	71.4	295	69.6	0.64	162	70.7	718	70.0	0.84	0.9	0.5	1.4	0.54
Severe MA dependence	23	82.1	143	77.3	352	81.3	0.50	166	77.9	352	81.3	0.31	189	78.4	847	80.6	0.45	0.8	0.5	1.4	0.49
Diagnoses																					
Conduct disorder	2	7.1	14	7.6	37	8.5	0.90	16	7.5	37	8.5	0.65	18	7.5	88	8.4	0.64	1.3	0.6	2.5	0.53
ASPD	7	25.0	37	20.0	77	17.8	0.56	44	20.7	77	17.8	0.38	51	21.2	191	18.2	0.28	1.2	0.7	2.1	0.44
Other substances																					
Nicotine dependence	18	64.3	123	66.5	286	66.1	0.97	141	66.2	286	66.1	0.97	159	66.0	695	66.1	0.96	0.9	0.6	1.4	0.55
Nicotine initiation	28	100	174	94.1	384	88.7	0.02*	202	94.8	384	88.7	0.01*	230	95.4	942	89.6	0.005*	3.9	1.6	9.7	0.003**
Alcohol dependence	4	14.3	45	24.3	137	31.6	0.04*	49	23.0	137	31.6	0.02*	53	22.0	319	30.4	0.01**	0.6	0.4	1.0	0.05
Alcohol flush syndrome	6	21.4	63	34.1	170	39.3	0.10	69	32.4	170	39.3	0.09	75	31.1	403	38.3	0.04*	0.7	0.5	1.1	0.11

MA = metha mphetamine, DBH = dopamine β-hydroxylase, ASPD = Antisocial personality disorder, OR = Odds ratio, 95% CI = 95% confidence interval

[a] Influence of DBH gene (TT/CT compared to CC) on identified risk and related factors on MIP after demographic, other diagnostic and MA-use variables and MIP were controlled.

[b] Compared to less severe MA use.

[c] During period of heaviest MA use.

* $p < 0.05$

** $p < 0.01$