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Depressive Symptom Severity-Related Clinical Characteristics in Korean Male Patients with Methamphetamine Use Disorder

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Abstract

Background: Methamphetamine (MA) use continually increases in world wide. MA users present diverse psychiatric comorbidities. The presence of these comorbid symptoms is positively correlated with poorer treatment outcomes and greater utilization of health care services. Depressive symptoms, in particular, are considered to be some of the most common psychiatric symptoms in this population Our study aimed to investigate depressive symptom severity-related clinical characteristics in male Korean methamphetamine (MA) users.

Methods: The inclusion criteria were as follows: (i) male; (ii) age ¡İ 18 years; (iii) a diagnosis of stimulant use disorder, especially for amphetamine-type substances, according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5); and (iv) positive urine test for MA at the time of admission. The exclusion criteria were as follows: (i) patients who were diagnosed with cognitive disorders, schizophrenia, schizoaffective disorder, or bipolar disorders; and (ii) patients who were diagnosed with significant physical illnesses, such as cerebrovascular, cardiovascular, or neurodegenerative diseases. Finally, a total of 200 Korean male patients with MA use disorder were included in our study. By reviewing the medical records of 200 male MA users hospitalized in a substance addiction treatment center of South Korea, the clinical characteristics in a MA abstinent state, including scores on the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Symptom Checklist-90-R Revised (SCL-90-R), and Korean Wechsler Adult Intelligence Scale (KWAIS) were collected. Analyses of covariances (ANCOVAs) for continuous variables and binary logistic regression analyses for discrete variables were used to compare the clinical characteristic scores among four groups that were defined by the severity of their depressive symptoms (i.e., minimal, mild, moderate, and severe).

Results: After adjusting for the effects of age, marital status, employment status, monthly income, age of first MA use, pursuit of euphoria, gastrointestinal symptoms, insomnia, hallucination, and cigarette smoking, a greater severity of depressive symptoms was significantly correlated with greater prevalence of aggression (adjusted odds ratio [aOR] = 2.065, P = 0.004) and irritability (aOR = 2.051, P = 0.001), greater scores on the BAI (F = 22.480, P < 0.0001) and all the items of SCL-90-R, and lower scores on the verbal intelligence quotient (F = 2.699, P = 0.047) of the KWAIS.

Conclusions: Our findings demonstrate a potential relationship between depressive symptom severity and other clinical characteristics among male patients with MA use disorder. Thus, depressive symptoms may be an important clinical concern for psychiatric treatment of MA users.

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methamphetamine (MA), depression, anxiety, verbal intelligence quotient, aggression, irritability

INTRODUCTION

Methamphetamine use continually increases in the countries in East and Southeast Asia [1]. According to the World Drugs Report [1] has shown that amphetamine-type stimulants are the second leading substances of abuse worldwide; estimates that up to 29 million individuals (0.6% in the global population between the ages of 15-64 years) have used amphetamine-type stimulants at least once in the past 12 months. The number of MA users in South Korea exceeded 20 of every 100,000 individuals in the general population in 2010, and this number has been continuously increasing. MA users accounted for 77.3% of newly identified drug users in 2016 in South Korea [2].

MA is a psychostimulant of the phenethylamine and amphetamine class, and addition of an extra methyl group

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to amphetamine yields methamphetamine, which has increased lipid solubility and crosses the blood-brain barrier more readily, thereby increasing the stimulant properties on the central nervous system [3]. MA induces diverse neurotoxic effects including damage to dopaminergic, noradrenergic, and serotonergic nerve terminals, as well as dysregulation of vesicular monoamine transporters. In addition, because MA induces neuronal apoptosis as well as activates astrocytes and microglia that lead to proinflammatory responses within the brain, a wide range of structural and functional changes within the central nervous can occur [3].

Because of these pharmacological properties, MA users present diverse psychiatric comorbidities including depression, psychosis, and anxiety [4]. Among MA users, the presence of these comorbid symptoms is positively correlated with poorer treatment outcomes and greater utilization of health care services. These comorbid symptoms are predictive of relapse to methamphetamine use following detoxification, and increase the risk of morbidity and mortality in MA users [5].

Depressive symptoms, in particular, are considered to be some of the most common psychiatric symptoms in MA users [6]. Zweben et al. [7] and Conway et al. [8] reported that 41.6% and 79.0% of MA users had depressive symptoms, respectively. Most importantly, comorbid depressive symptoms can result in fewer benefits from long-term psychotherapy and decreased treatment retention among MA users, a lower quality of life, and increased risk of suicidal behavior [9,10]. Moreover, failure to manage depressive symptoms may lead to high rates of relapse in the first several weeks of abstinence from MA [11]. Thus, we aimed to investigate the relationship between depressive symptom severity-related clinical characteristics in Korean male patients with MA use disorder.

METHODS

Study Overview and Subjects

By reviewing the medical records of male inpatients diagnosed with MA use disorder from January 2016 to April 2019 at Bugok National Hospital in Gyongsangnam, Republic of Korea, the clinical characteristics of the study subjects were collected retrospectively. Bugok National Hospital has an addiction treatment center that has a specialized rehabilitation program for male inpatients with MA use disorder. The inclusion criteria were as follows: (i) male; (ii) age ≥ 18 years; (iii) a diagnosis of stimulant use disorder, especially for amphetamine-type substances, according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [12]; and (iv) positive urine test for MA at the time of admission. The exclusion criteria were as follows: (i) patients who were diagnosed with cognitive disorders, schizophrenia, schizoaffective disorder, or bipolar disorders; and (ii) patients who were diagnosed with significant physical illnesses, such as cerebrovascular, cardiovascular , or neurodegenerative diseases.

At the time of admission, the demographic and clinical characteristics of each subject were recorded based on interviews with psychiatrists and mental health professionals. Since acute withdrawal symptom induced by MA can last for about 7-10 days [13], the withdrawal symptoms occurring within 10 days were recorded based on length of abstinence. For the purpose of adjusting the potential impacts of MA withdrawal symptoms on the current clinical manifestations, the psychometric scales were assessed over the 14th day after hospitalization of each of the subjects. The study participants voluntarily agreed to participate in the survey, and written informed consent was obtained after the purpose and methodology of the study were explained to them. The study was approved by the Institutional Review Board (BNH IRB No. 2019-10) of Bugok National Hospital, Chanyong, Gyeongsangnam, Republic of Korea. All private information was coded and limited for use in this study. Finally, a total of 200 Korean male patients with MA use disorder were included in this study.

MEASUREMENTS

Demographic and Clinical Characteristics

We collected patient demographic characteristics, including age, marital status, educational attainment, military service, and monthly income, and MA use-related characteristics including age at first MA use, dose (highest dosages used in the time prior to hospitalization), frequency, duration of MA use, cause of the first MA use, cigarette smoking, and alcohol drinking. In addition, we collected data related to MA withdrawal symptoms, including gastrointestinal symptoms, headache, insomnia, anxiety, depression, and hallucinations, which were evaluated with supplementary use of the Methamphetamine Withdrawal Questionnaire (MAWQ) [13].

In addition, the clinical characteristics associated with suicide (prior suicidal attempt, current suicidal ideation) were collected, and aggression, irritability, and impulsivity over the previous month were evaluated based on the following definitions: aggression was defined as “hostile, injurious, or destructive behavior” according to Siever [14]; irritability was defined as being “easily annoyed and provoked to anger” according to Stringaris et al. [15]; impulsivity was defined as “a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard of negative consequences for themselves or others” according to Moeller et al [16].

Psychometric Scales

Several psychometric scales were used to assess depressive symptoms including the Beck Depression Inventory-II (BDI-II) [17], the Beck Anxiety Inventory (BAI) [18], the Symptom Checklist-90-Revised (SCL-90-R) [19], and the short form of the Korean Wechsler Adult Intelligence Scale (KWAIS) [20]. The BDI is a 21-item self-questionnaire to evaluate the severity of depressive symptoms [17]. Each of the items can evaluate the state that best matches how

the respondent has felt during the previous two weeks, based on a four point Likert-type scale (scoring range = 0–3). The BDI has been formally translated into Korean, and the reliability and validity of its Korean version were previously confirmed (Cronbach's α = 0.94) [21]. The BAI is a 21-item self-questionnaire to evaluate the severity of anxiety symptoms [18]. Each of the items can evaluate the state that best matches how the respondent has felt during the previous two weeks, based on a four point Likert-type scale (scoring range = 0–3). The BAI has been formally translated into Korean, and the reliability and validity of its Korean version were previously confirmed (Cronbach's α = 0.93, r = 0.84) [22]. The Symptom Checklist-90-Revised (SCL-90-R) is a 90-item self-questionnaire to assess multi-dimensional symptoms and distress [19]. Respondents rate their current level of symptoms experienced during the last seven days on a scale of 0-4. The SCL-90-R has nine subscale symptom domains associated with somatization, obsessive–compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. The SCL-90-R had been formally translated into Korean, and the reliability and validity of its Korean version were previously confirmed [23]. Finally, we used the short form of the KWAIS designed by Silverstein [20], which consists of two subtests for verbal and performance intelligence quotients. It has been identified to be highly correlated with general and Full Scale intelligence quotients (IQ) (r = 0.91) [24].

Statistical Analyses

According to the depressive symptom classifications in the DSM-5 for the BDI-II, the participants were divided into four groups based on their score: minimal (0-13), mild (14-19), moderate (20-28), and severe (29-63) [25]. Using analyses of covariance (ANCOVAs) for continuous variables and binary logistic regression analyses for discrete variables, differences in baseline and clinical characteristics among the four groups were evaluated after adjusting for the effects of confounding variables. *Post-hoc* analyses for continuous variables were used, employing Fisher's Least Significant Difference tests. Statistical significance was set at $P < 0.05$ (two-tailed) in all tests. All statistical analyses were performed with IBM SPSS Statistics (Statistical Package for the Social Sciences) 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline Characteristics of the Participants with Methamphetamine Use Disorder

As shown in **Table 1**, the percentages of the individual depressive symptom severity groups among 200 male patients with methamphetamine use disorder were 19.5% for "minimal", 11.5% for "mild", 19.5% for "moderate", and 49.5% for "severe". In the context of these baseline characteristics, there were significantly younger ages (F [3,199] = 3.914, $P = 0.010$) and younger age of first methamphetamine use (F [3,199] = 3.045, $P = 0.030$) in the more severe depressive symptom groups. Moreover, there were significantly smaller proportions of married persons ($x^2 = 11.706$, $P = 0.008$), employed persons ($x^2 = 8.557$, $P = 0.036$), persons with monthly income more than $2,000 USD ($x^2 = 16.538$, $P = 0.001$), and cigarette smoking ($x^2 = 9.327$, $P = 0.025$) and significantly greater proportions for pursuit of euphoria ($x^2 = 15.268$, $P = 0.002$) (in terms of the cause of first methamphetamine use), gastrointestinal symptoms ($x^2 = 9.011$, $P = 0.029$), insomnia ($x^2 = 11.604$, $P = 0.009$), and hallucination ($x^2 = 8.410$, $P = 0.038$) (in terms of methamphetamine withdrawal symptoms) in the more severe depressive symptom groups. In view of these findings, we analyzed the differences between the four depressive symptom severity groups using ANCOVAs for continuous variables and binary logistic regression analyses for discrete variables, while adjusting for the effects of age, marital status, employment, monthly income, age of first MA use, pursuit of euphoria, gastrointestinal symptoms, insomnia, hallucination, and cigarette smoking.

After adjusting for the effects of the confounding variables, there were no significant trends among the depressive symptom severity groups with respect to educational attainment (adjusted odds ratio [aOR] = 1.017, $P = 0.916$), military service (aOR = 0.807, $P = 0.226$), duration of methamphetamine use (F [3,199] = 0.290, $P = 0.832$), dose of methamphetamine per day (F [3,199] = 0.491, $P = 0.689$), frequency of methamphetamine use per week (aOR = 0.914, $P = 0.575$), prior hospitalization due to methamphetamine use (aOR = 0.857, $P = 0.371$), curiosity (aOR = 1.128, $P = 0.450$), escape from a sense of emptiness (aOR = 1.146, $P = 0.424$), alleviation of psychological distress (aOR = 1.266, $P = 0.247$), and socialization with friends (aOR = 1.145, $P = 0.398$), cause of first methamphetamine use, headache (aOR = 0.828, $P = 0.700$), anxiety (aOR = 1.056, $P = 0.932$) and depression (aOR = 1.191, P = 0.452) related to methamphetamine withdrawal symptoms, or alcohol drinking (aOR = 1.122, P = 0.434).

Clinical Characteristics of the Participants with Methamphetamine Use Disorder

As shown in **Table 2**, after adjusting for the effects of the confounding factors, there were significantly greater scores of aggression (aOR = 2.065, $P = 0.004$) and irritability (aOR = 2.051, $P = 0.001$), significantly greater scores on the BAI (F [3,199] = 22.480, $P < 0.0001$), somatization (F = 15.118, $P < 0.0001$), obsessive-compulsive (F [3,199] = 13.646, $P < 0.0001$), interpersonal sensitivity (F [3,199] = 19.900, $P < 0.0001$), depression (F [3,199] = 42.312, $P < 0.0001$), anxiety (F = 25.799, $P < 0.0001$), hostility (F [3,199] = 17.597, $P < 0.0001$), phobia (F [3,199] = 19.239, $P < 0.0001$), paranoid ideation (F [3,199] = 17.566, $P < 0.0001$), and psychoticism (F [3,199] = 18.702, $P < 0.0001$) on the SCL-90-R, and significantly lower verbal intelligence quotients (F [3,199] = 2.699, $P = 0.047$) based on the KWAIS in the more severe depressive symptom groups.

Conversely, after adjusting for the effects of the confounding factors, there were no significant differences among the

depressive symptom severity groups with respect to suicide attempts (aOR = 0.287, *P* = 1.235), suicidal ideation (aOR = 0.065, *P* = 1.488), impulsivity (aOR = 1.504, *P* = 0.185), or performance intelligence (F [3,199] = 0.206, *P* = 0.892) and Full Scale intelligence quotients (F [3,199] = 1.690, *P* = 0.171) based on the KWAIS.

Table 1. Depressive symptom severity-related baseline characteristics of male patients with methamphetamine use disorder

	Depressive symptom severity							
	Total sample (n = 200)	Minimal (n = 39)	Mild (n = 23)	Moderate (n = 39)	Severe (n = 99)	Statistical coefficient	*P*-value	Adjusted *P*-value†
Age, mean (SD) years	44.4 (7.4)	45.5 (7.1)	46.4 (8.3)	45.6 (7.1)	42.3 (7.0)	F = 3.914	0.010 (a = b = c > d)‡	-
Married, n (%)	58 (29.0)	14 (35.9)	9 (39.1)	17 (43.6)	18 (18.2)	x^2 = 11.706	0.008	-
Above high school, n (%)	126 (63.0)	25 (64.1)	13 (56.5)	24 (61.5)	64 (64.6)	x^2 = 0.585	0.900	0.916
Military service, n (%)	93 (46.5)	20 (51.3)	14 (60.9)	13 (33.3)	46 (46.5)	x^2 = 4.985	0.173	0.226
Employed, n (%)	96 (48.0)	25 (64.1)	13 (56.5)	20 (51.3)	38 (38.4)	x^2 = 8.557	0.036	-
Age of first MA use, mean (SD) years	27.5 (9.1)	29.3 (9.9)	28.4 (9.9)	30.0 (8.1)	25.7 (8.7)	F = 3.045	0.030 (a = b = c > d)‡	-
Duration of MA use, mean (SD) months	94.5 (64.5)	86.4 (56.7)	98.4 (61.9)	94.2 (65.6)	97.0 (68.1)	F = 0.280	0.840	0.832
Dose of MA use/day, mean (SD) g	0.5 (0.3)	0.4 (0.3)	0.6 (0.4)	0.4 (0.3)	0.6 (0.3)	x^2 = 2.476	0.063	0.689
Twice or more use of MA/week, n (%)	149 (74.5)	26 (66.7)	18 (78.3)	26 (66.7)	79 (79.8)	x^2 = 4.153	0.245	0.575
Prior hospitalization due to MA use, n (%)	139 (69.5)	25 (64.1)	16 (69.6)	27 (69.2)	71 (71.7)	x^2 = 0.767	0.867	0.371
Cause of MA use of first time Curiosity, n (%)	65 (32.5)	13 (33.3)	4 (17.4)	13 (33.3)	35 (35.4)	x^2 = 2.785	0.426	0.450
Pursuit of euphoria, n (%)	85 (42.5)	7 (17.9)	12 (52.2)	14 (35.9)	52 (61.2)	x^2 = 15.268	0.002	-
Escape from a sense of emptiness, n (%)	70 (35.0)	11 (28.2)	6 (26.1)	12 (30.8)	41 (41.4)	x^2 = 3.692	0.297	0.424
Alleviate psychological distress, n (%)	44 (22.0)	6 (15.4)	2 (8.7)	11 (28.2)	25 (25.3)	x^2 = 4.852	0.183	0.247
Socialize with friends, n (%)	66 (33.0)	10 (15.2)	6 (26.1)	13 (19.7)	37 (37.4)	x^2 = 2.311	0.510	0.402
MA withdrawal symptoms								
Gastrointestinal symptoms, n (%)	33 (16.5)	1 (2.6)	6 (26.1)	5 (12.8)	21 (21.2)	x^2 = 9.011	0.029	-
Headache, n (%)	18 (9.0)	3 (7.7)	1 (4.3)	3 (7.7)	11 (11.1)	x^2 = 1.309	0.727	0.700
Insomnia, n (%)	86 (43.0)	14 (35.9)	13 (43.5)	9 (23.1)	53 (53.5)	x^2 = 11.604	0.009	-
Anxiety, n (%)	109 (54.5)	18 (46.2)	10 (43.5)	18 (46.2)	63 (63.6)	x^2 = 6.650	0.084	0.932
Depression, n (%)	50 (25.0)	11 (28.2)	3 (15.4)	6 (15.4)	30 (30.3)	x^2 = 5.375	0.146	0.452
Hallucination,, n (%)	113 (56.5)	19 (48.7)	10 (43.5)	18 (46.2)	66 (33.0)	x^2 = 8.410	0.038	-
Cigarette smoking, n (%)	162 (81.0)	36 (92.3)	14 (60.9)	32 (82.1)	80 (80.8)	x^2 = 9.327	0.025	-
Alcohol drinking, n (%)	90 (45.0)	15 (38.5)	7 (30.4)	20 (51.3)	48 (48.5)	x^2 = 3.753	0.289	0.434

MA, methamphetamine

† Adjusted for effects of age, marital status, employment, monthly income, age of first MA use, pursuit of euphoria, gastrointestinal symptoms, insomnia, hallucination, and cigarette smoking
‡ Post hoc analysis: a, minimal; b, mild; c, moderate; d, severe

Table 2. Depressive symptom severity-related clinical characteristics of male patients with methamphetamine use disorder

	Depressive symptom severity							
	Total sample (n = 200)	Minimal (n = 39)	Mild (n = 23)	Moderate (n = 39)	Severe (n = 99)	Statistical coefficient	*P*-value	Adjusted *P*-value†
Suicidal attempt, n (%)	43 (21.5)	5 (12.8)	1 (4.3)	16 (41.0)	21 (21.2)	$x^2 = 14.565$	0.002	0.287
Suicidal ideation, n (%)	39 (19.5)	4 (10.3)	1 (4.3)	12 (30.8)	22 (22.2)	$x^2 = 9.109$	0.028	0.065
Aggression, n (%)	38 (19.0)	3 (7.7)	3 (13.0)	4 (10.3)	28 (28.3)	$x^2 = 11.251$	0.010	0.004
Irritability, n (%)	50 (25.0)	4 (10.3)	5 (21.7)	5 (12.8)	36 (36.4)	$x^2 = 14.555$	0.002	0.001
Impulsivity, n (%)	20 (10.0)	2 (5.1)	3 (13.0)	4 (10.3)	11 (11.1)	$x^2 = 1.404$	0.705	0.185
Beck Anxiety Inventory, mean (SD)	18.4 (14.8)	5.3 (8.7)	12.3 (9.9)	15.0 (11.2)	26.4 (14.0)	F = 32.630	< 0.0001	< 0.0001 (a = b < c < d)‡
Symptom Checklist-90-R								
Somatization, mean (SD)	58.0 (14.8)	45.8 (10.3)	51.5 (9.8)	56.4 (14.9)	64.8 (13.5)	F = 23.242	< 0.0001	< 0.0001 (a = b < c < d)‡
Obsessive-compulsive, mean (SD)	57.4 (13.6)	46.5 (8.5)	50.5 (10.8)	56.9 (15.6)	63.5 (11.3)	F = 22.792	< 0.0001	< 0.0001 (a = b < c = d)‡
Interpersonal sensitivity, mean (SD)	58.7 (13.6)	46.6 (8.4)	52.8 (10.8)	55.8 (12.1)	66.1 (11.8)	F = 32.707	< 0.0001	< 0.0001 (a =b < c < d)‡
Depression, mean (SD)	62.2 (14.2)	46.5 (5.9)	54.9 (8.5)	59.0 (12.2)	71.4 (11.1)	F = 62.099	< 0.0001	< 0.0001 (a < b = c < d)‡
Anxiety, mean (SD)	60.0 (14.4)	45.1 (7.6)	54.9 (11.3)	57.0 (12.3)	68.2 (12.0)	F = 42.554	< 0.0001	< 0.0001 (a < b = c < d)‡
Hostility, mean (SD)	56.2 (13.2)	45.6 (8.9)	48.2 (9.0)	55.8 (13.0)	62.3 (12.2)	F = 24.305	< 0.0001	< 0.0001 (a = b < c < d)‡
Phobia, mean (SD)	60.1(15.3)	45.7 (6.6)	54.5 (10.8)	56.8 (12.1)	68.4 (15.10	F = 32.600	< 0.0001	< 0.0001 (a < b = c < d)‡
Paranoid ideation, mean (SD)	59.0 (14.5)	46.7 (8.4)	56.3 (8.9)	51.3 (10.1)	65.5 (14.8)	F = 27.240	< 0.0001	< 0.0001 (a < b = c < d)‡
Psychoticism, mean (SD)	60.3 (15.2)	48.3 (9.4)	56.4 (11.6)	55.7 (12.0)	67.8 (14.9)	F = 24.204	< 0.0001	< 0.0001 (a < b = c < d)‡
Wechsler Adult Intelligence Scale								
Verbal intelligence quotient, mean (SD)	9.6 (2.4)	10.0 (2.8)	8.8 (2.2)	8.9 (2.1)	9.1 (2.2)	F = 1.828	0.143	0.047 (a > b = c = d)‡
Performance intelligence quotient, mean (SD)	9.2 (2.3)	9.8 (2.2)	9.9 (2.9)	8.7 (1.9)	9.8 (2.5)	F = 2.096	0.102	0.892

DISCUSSION

Our study demonstrates that groups with greater severity of depressive symptoms had significantly greater rates of aggression and irritability, greater scores on the BAI, greater scores on somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobia, paranoid ideation, and psychoticism items on the SCL-90-R, and lower scores on the verbal intelligence quotient of the KWAIS. About 68% of study subjects were classified as having moderate to severe levels of depressive symptoms. In addition a greater severity of depressive symptoms was significantly related to higher rates of aggression and irritability and greater scores on the BAI and SCL-90-R.

This finding is consistent with previous studies that have shown that the prevalence of depression ranged from 28%-80% among amphetamine-type stimulant users or amphetamine-type stimulant-dependent patients seeking treatment [4-8]. Bao et al. [6] identified a dose-response relationship between duration of MA use and risk of co-occurring depressive and anxiety-related symptoms. Indeed comorbid depressive symptoms of MA users are caused by various factors such as comorbid other psychiatric symptoms, low quality of life, and severity and duration of withdrawal symptoms [4]. Furthermore, depressive symptoms are often difficult to distinguish clearly from other psychiatric symptoms, so the rate of comorbid depressive symptoms of MA users tends to have a large deviation depending on research [6]. A clear mechanism through which MA causes Depression and other psychiatric symptoms have yet to be identified; however, MA-induced neurotoxicity is thought be responsible. Use of MA results in a depletion of monoamine stores, down-regulation of synaptic receptors, and irreversible loss of nerve terminals and neuronal cell bodies [3,26]. Also, reduced white matter integrity and reduced gray matter volume in the cingulate, limbic, and paralimbic cortices associated with depressive and other psychiatric symptoms are more prevalent among frequent MA users compared to healthy controls [26]. Moreover, exposure to MA may deplete glutathione (GSH) stores and increase oxidized glutathione (GSSG) levels in the striatum; this reduction in the ratio of GSH to GSSG inhibits the activity of the

mitochondrial respiratory chain complex that is considered to play a crucial role in the pathogenesis of depression [27]. Consequently, the affective and motivational dysfunction associated with depressive symptoms can occur as a result of MA toxicity, whereas the unremitted depressive symptoms can contribute to sustained use of drugs in greater amounts at a higher frequency in order to relieve depressive symptoms [28]. Depression and other psychiatric symptoms including aggression, irritability, and anxiety may share a neurochemical basis, and extensive MA-induced alterations in the function of serotonin, dopamine, and neuropeptide systems such as those regulated by corticotropin-releasing factor (CRF) may lead to various psychiatric symptoms [3,29]. Indeed, there appears to be a clear relationship between duration of MA use and extent of the dysfunction in both dopaminergic and serotonergic systems [29,30]. A MA-induced decrease of serotonergic function may be associated with increased aggression and irritability among violent men or offenders [31]. In animal models, an increase in CRF in the amygdala is responsible for the reinstatement of MA-induced irritability [32], and CRF receptor antagonism reduces depression and anxiety during amphetamine withdrawal [33]. Similarly, MA-induced neurobiological alterations may be caused not only depression but also aggression, irritability, and anxiety [28-33]. Thus, the positive relationship between depressive symptoms and other psychiatric symptoms is supported by the previous findings.

Indeed, we observed that greater severity of depressive symptoms was significantly related to lower scoring on the verbal intelligence quotient of the KWAIS. It is known that MA-induced neurotoxicity is associated with cognitive changes, such as memory deficits associated with reduced dopamine and serotonin transporter density [29,30]. Pervasive effects on the medial basal forebrain, the hippocampus, and the prefrontal cortex represent noradrenergic regions related to cognitive decline [34]. With respect to the specific cognitive domains potentially affected, a meta-analysis of 18 studies found moderate effects of MA use disorder on several cognitive processes including episodic memory, executive functions (e.g., response inhibition, novel problem solving), complex information processing speed, and psychomotor functions [35]. Furthermore, it is suggested that MA-induced neurocognitive decline also overlaps with the pathophysiology of depression, aggression, and anxiety [35].

In our findings, depression symptom severity was not significantly related with impulsivity, though it has been reported that abuse of psychostimulants is linked to heightened impulsivity.[36] However, a recent study investigating the relationship between the severity of MA use-related problems and measures of impulsivity in non-treatment-seeking individuals who reported regular MA use (n = 177) revealed that greater severity of MA use is associated with greater self-reported impulsiveness, but observed no relationship with behavioral measures of impulsivity [36]. Other current findings also suggest that impulsivity does not reflect the severity of MA use [37]. Moreover, it is speculated that acute intoxication and craving may confound impulsivity measures, such as performance of response inhibition and delay [37]. In our findings, there was no significant association between depression and prior suicidal attempts or current suicidal ideation. It is well known that suicide is more prominent among female drug users than male drug users [10], though our study included only male MA users. A Swedish cohort study of 39 MA users demonstrated that 10 out of 15 deaths were caused by "acute drug use," and only one death resulted from suicide [38]. Cause of death in MA users may be due to overdose of another drug or accident [38,39]. Therefore, it is speculated that MA use and suicidality may be poorly inter-related. Remarkably, in our findings, the depressive symptom severity was not been significantly related to MA withdrawal. It is known that depressive symptomology is a hallmark of MA withdrawal. However, duration of MA withdrawal symptoms was shorter than 10 days [13]. Severity of MA withdrawal syndrome appears to be related with the frequency of use, yet the syndrome resolves spontaneously within the first week of abstinence [40]. Thus, it can be speculated that the depressive symptoms in a MA abstinent state may be distinct from the depressive symptoms in a MA withdrawal state.

Our study has several limitations as follows. First, only MA users hospitalized in a clinical center in South Korea were included. Therefore, our findings may not be generalizable to all MA users. Second, the prior psychiatric and MA use histories were evaluated based solely on self-reports, which may have resulted in an increased risk of recall bias. Third, the inter-rater reliability for aggression, impulsivity, irritability, and other clinical characteristics were not evaluated. Fourth, the familywise error rates due to multiple comparisons were not reduced. Despite these limitations, our study adds to the literature of depressive symptom severity-related clinical characteristics in Korean male patients with MA use disorder. These depressive symptoms may be an important target for proper psychiatric management of MA users.

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