

A comparison of pattern of psychiatric symptoms in inpatients with bipolar disorder type one with & without methamphetamine use

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Abstract

Background: Iran is facing an outbreak of methamphetamine-induced disorders and frequent use of these substances in patients with bipolar disorder. Using or intoxication of methamphetamine in patients with bipolar I disorder may alter the patient's clinical profile; however there is limited studies about impact of methamphetamine on clinical manifestation of bipolar disorders. This study aimed to compare psychiatric symptoms in patients with bipolar I disorder with and without concomitant use of methamphetamine.

Methods: In a cross-sectional study, psychiatric symptoms of bipolar I disorder in patients with (Meth+) and without (Meth-) methamphetamine use was evaluated. A number of 57 participants with Meth+ and 50 subjects with Meth- were recruited. The clinical picture of bipolar disorder was investigated by Young Mania Rating Scale (YMRS), 17-item Hamilton Depressive Rating Scale (HDRS-17) and the Scale for Assessment of Positive Symptoms (SAPS). Statistical comparisons were performed using the T-test for independent samples and Mann-Whitney test.

Results: There was no statistically significant difference between two groups regarding age, duration of illness and hospitalizations. However, male participants were significantly higher in Meth+ group than in Meth- one ($p < 0.001$). The mean (\pm SD) scores in the two groups of Meth+ and Meth- for YMRS, HDRS, and SAPS were 31.3 (± 1.3) and 34.0 (± 1.2), 13.7 (± 0.7) and 13.5 (± 0.5), and 50.0 (± 1.9) and 48.0 (± 2.1), respectively, which were not statistically significant ($p < 0.05$).

Conclusion: There was no significant difference in the overall clinical manifestation of bipolar I disorder in patients with and without methamphetamine use. However, in some symptomatology domains, there were some differences between the two groups.

Keywords: Bipolar one disorder, Methamphetamine, Manic episode, Psychosis.

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Introduction

In the recent years, most countries are facing marked increase in methamphetamine abuse (1,2). In Iran methamphetamine abuse has also had an increasing trend in current years, with no registered record of its abuse in 2003 to 3.7% in 2006 as the most common abused drug (3).

A large group of methamphetamine users

includes people with chronic psychiatric diseases such as bipolar mood disorder (4). Based on Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study in 2006, about %13 of patients with bipolar disorder, reported a history of abuse of at least one substance including marijuana, cocaine, amphetamines, PCP, LSD and opiates, respectively (5).

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Accordingly, in another study on 100 patients with methamphetamine dependence, the rate of co-morbid psychiatric diseases was 36%, of which 16% belonged to mood disorders; while psychosis and anxiety disorders were reported in next rankings (%13 and %7, respectively). The authors believed that these finding shows a necessity for an integrated healthcare model that also covers drug abuse disorders and associated psychiatric diseases (6).

A significant part of literature has showed different psychiatric manifestations associated with methamphetamine use. For instance, in a study in South Africa on psychiatric admissions related to methamphetamine use, the most common psychiatric presentation was combination of aggressive behaviors and paranoid delusions with a prevalence rate of %30. Aggressive behavior in men was twice of that for women. Women showed a greater extent of changes in mood such as depressed mood, euphoria and ecstasy. There was no significant gender difference in the incidence of other symptoms. A percentage %12 of methamphetamine-induced psychosis cases also suffered from bipolar disorder (7).

In another study in Iran, the prevalence of psychotic symptoms in patients with methamphetamine induced psychotic disorders included 82% persecutory delusion, 70.3% auditory hallucination, 57.7% attributable delusions, 44.1% visual hallucinations, 39.6% grandiosity delusions, and 26.1% jealousy delusion, which was similar to the first methamphetamine epidemic report in Japan (8).

Additionally, in a study on 278 cases of methamphetamine dependency, a dose-related increase in aggressive behavior independent of the psychotic symptoms was seen in methamphetamine users compared to non-user counterparts (9).

In addition to a variety of disorders caused by substances, substance abuse can complicate the clinical profile of bipolar I disorder which may lead to higher rate of mixed and dysphoric state, higher rate of hospitalization and relapse and increase in

suicidal attempts (10). Despite a marked number of researches on methamphetamine induced psychiatric disorders, there is a paucity of research regarding impact of methamphetamine use on bipolar disorder presentation. Most studies on clinical profile of bipolar I disorder patients with concurrent substance abuse are based on alcohol or mixed drug consumption (11,12) even though significant users of methamphetamine are among patients with bipolar disorders.

Given the rapid increase of methamphetamine abuse in Iran (3,13-16), physical and psychological problems caused by this substance (15), and different demographics of bipolar I disorder in Iranian sample (17), a nationwide study on various aspects of methamphetamine use on bipolar disorder seems inevitable. This line of research may provide thorough information for future interventions. Therefore, we aimed to compare the clinical symptoms of manic /mixed episodes in patients with bipolar I disorder in those with (Meth+) and without (Meth-) amphetamine use prior to recurrence of the episode. The finding of the current study might help precise diagnosis and proper treatment selection when we have comorbid methamphetamine use disorder and bipolar I disorder and we are not certain about the etiology of psychiatric symptoms.

Methods

Participants and procedure

In this study 107 participants were recruited from patients with bipolar I disorder who were hospitalized in Iran Hospital of Psychiatry (7th km of Tehran- Karaj road) from early summer of 2012 to the end of summer of 2014. Reason for admission was relapse of manic or mixed episode. Participants entered the study through sequential, non-randomized sample selection based on inclusion criteria.

Diagnosis of bipolar I disorder was considered according to DSM-IV-TR during the hospitalization by a trained resident of psychiatry and it was approved by a psychiatric professor. Individuals who were

diagnosed with bipolar I disorder as their first diagnosis by both the resident and psychiatric professor were included in the study. Those with controversial diagnosis between the psychiatry resident and the related professor and those whom their diagnosis changed during hospitalization were excluded.

Patients and their family members were asked about pattern of methamphetamine use, the recent use of methamphetamine and it was furtherly confirmed through screening urine toxicology. Considering false positive reports in urine toxicology, cases with discordant history or urine toxicology reports were excluded from the study.

All of the patients were evaluated for taking other drugs, at least in the last 6 months, by history taking and urine toxicology. Cases with positive results of substances other than methamphetamine were excluded from the study to eliminate confounding factors. Patients and their family members were also asked about their hospitalization records and the approximate duration of bipolar I disorder.

After considering the inclusion and exclusion criteria, all the remaining patients were evaluated and scored within 48 hours from admission (to avoid influence of the medication on their symptomatology and their responses) by the questionnaires Young Mania Rating Scale (Y-MRS), Hamilton Depression Rating Scale (HDRS-17) and Scale for the Assessment of Positive Symptoms (SAPS) in terms of mood, psychomotor, vegetative, behavioral and psychotic symptoms including types of hallucinations and delusions and thought disorders. Each item was scored based on the patient and family members' responses, clinical observations and nurses' reports. Cases were followed during their hospitalization and those with the most concordant subjective and objective evaluation by a third year trained resident entered the study.

The inclusion criteria were 1) signing the written consent by the patient or their family; 2) diagnosing bipolar I disorder with

relapse of mania or mixed episode by a resident of psychiatry, confirmed by a professor of psychiatry; 3) the use of methamphetamine in Meth+ patients based on the individual and family members' reports, confirmed by the urine toxicology tests; 4) lack of methamphetamine use history in Meth- patients, according to the individual, and family members' reports, confirmed by urine toxicology tests.

The exclusion criteria were: 1) comorbidity with personality disorders according to the interview with the patient and family members conducted by a professor of psychiatry and previous medical records if any (given the overlapping of symptoms in personality disorders and bipolar I disorder), 2) ruling out the diagnosis of bipolar I disorder by a psychiatry resident confirmed by a professor of psychiatry; 3) the existence of other major neurological diseases such as epilepsy, brain tumors and dementia, based on an interview with the patient and family members and the medical records; 4) the use of other substances, including opioids, other stimulants, hallucinogens and alcohol in any degree during recent 6 months, according to the individual and family reports, confirmed by urine toxicology tests.

Questionnaires

Y-MRS: This questionnaire was developed by Young et al to measure the severity of mania and its validity and reliability has been determined. The questionnaire has 11 options, each option scoring from 0 to 4. Total score can be within 0 and 60. The questionnaire is able to assess the severity of mania along with assessment of response to treatment and detection of recurrence. Test reliability coefficient of 0.8 and a correlation coefficient of 0.91 were measured (18). The questionnaire was translated by Barekatin et al into Farsi and adequate psychometric properties were shown (19). According to this study, Cronbach's alpha was 0.72, reliability coefficient of patients was 0.63 and inter rater reliability was rated 0.96.

SAPS: This questionnaire was designed by Andreasen to assess the severity of psychotic positive symptoms and its validity and reliability has been confirmed (20). The questionnaire is used to assess the positive symptoms of schizophrenic patients in four areas: hallucinations, delusions, thought disorder, and bizarre behavior. The scale maintains 30 questions, each based on a Likert scale rating 0 to 5 and the total scale score of within 0 and 150. Acceptable validity of the test is shown by examining its correlation with the severity assessment scales and its reliability was measured by trained interviewers and it was rated good to excellent. In Iran retest reliability of the scale has been reported 0.77 and its Cronbach's alpha coefficient was 0.83. Another study listed the retest reliability coefficient of the scale as 0.89.

HDRS-17: This questionnaire was developed by Hamilton to measure the severity of depressive symptoms and its consistency was indicated through two methods of test-retest reliability and parallelism with internal Cronbach's alpha of 0.66 and 0.65, respectively (21). The questionnaire consists of 17 options including 8 signs of physical complaints, 5 signs of behavioral problems, 2 signs of cognitive complaints, and finally 2 signs are related to changes in patients' emotions. Each item is scored from 0 to 4, and its overall score is within 0 to 76. Scores within 8 to 13 indicates mild depression and 14 to 18 shows major average depression and higher than 18 is indicator of severe depression.

Data analysis Design

Table 1. Demographic description in patients with bipolar I disorder with and without methamphetamine use (Meth +, Meth - respectively)

Variable	Category	Meth+ Group (N, %)	Meth- Group (N, %)	Chi-square test
Gender	Male	56(98.2)	36(72.0)	p<0.001 X ² =15.222
	Female	1(1.8)	14(28.0)	
Education	Under graduated	33(57.9)	19(38.0)	p=0.031 X ² =6.963
	Diploma	22(38.6)	23(46.0)	
Employment	University	2(3.5)	8(16.0)	p=0.966 X ² =0.069
	Jobless with no income	39(68.4)	35(70.0)	
	Jobless with an income	2(3.5)	2(4.0)	
	Employed	16(28.1)	13(26.0)	

Data were analyzed through SPSS v.22 statistical software. Qualitative data were described by frequency (number and percentage) and quantitative ones by mean, standard deviation, standard error of the mean, median, and range. In case of ordinal variables, in order to facilitate statistical comparisons, the mean and standard error was also mentioned. To compare two groups, chi-square test, independent t-test and the Mann-Whitney test were used. P-value of less than 0.05 was considered statistically significant.

Results

A number of 57 patients entered in methamphetamine user group (Meth+) and a number of 50 ones in non-user group (Meth-). Methamphetamine users included 32 methamphetamine dependents (56.1%), 20 abusers (35.1%) and 5 individual users who did not suffer from methamphetamine-induced disorders (including dependence or abuse) (8.8%). The mean age (\pm SD) of Meth+ group was 35.3(\pm 9.1) years (median 32 years, range 19 to 57 years) and the mean age (\pm SD) of Meth- group was 32.5 (\pm 9.4) years (median 31 years; range 20 to 61 years) (t-test: $t=1.535$; $p=0.128$). Other demographic information of the participants is shown in Table 1. As seen in this table, male to female ratio was significantly higher in Meth+ group than in Meth- group. Patients in the Meth+ group had lower education in comparison to meth- group, but rate of occupation in two groups was not significantly different.

Meth+ patients had an average hospitalization record of 2.4 times (including recent

Table 2. Scores of Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HDRS) and the Scale for Assessment of Positive Symptoms (SAPS) in patients with bipolar I disorder with and without methamphetamine use (Meth +, Meth - respectively)

Inst	Methamphetamine user group				Methamphetamine non-user group				T test	
	Mean (±SD)	Mean standard error	Median	Range	Mean (±SD)	Mean standard error	Median	Range	T	p
YMRS	31.3 (9.7)	1.3	35	18-50	34.0 (8.4)	1.2	27	14-51	-1.539	0.127
HDRS	13.7 (5.5)	0.7	12	7-26	13.5 (4.3)	0.6	10	7-35	1.808	0.182
SAPS	50.0 (14.6)	1.9	55	14-48	48.0 (14.8)	2.1	58	9-87	0.396	0.531

Table 3. Scores of Young Mania Rating Scale titles (YMRS) in patients with bipolar I disorder with and without methamphetamine use (Meth +, Meth - respectively)

YMRS	Methamphetamine user group (Meth+)				Methamphetamine Non-user group (Meth-)				P (Mann-Whitney test)
	Mean	Standard Error	Median	Mode	Mean	Standard Error	Median	Mode	
Elevated mood	2.6	0.14	3	3	2.7	0.15	3	3	0.446
Increased activity/ energy	2.8	0.14	3	3	2.8	0.14	3	3	0.698
Sexual Interest	1.5	0.12	2	2	1.3	0.09			0.199
Sleep	2.9	0.11	3	3	2.9	0.09	3	3	0.862
Irritability	3.7	0.30	4	4	3.6	0.29	4	2	0.675
Speech	5.1	0.27	5	4	4.3	0.29	4	2	0.039
Language/Thought disorder	2.5	0.13	3	3	6.2	0.11	3	2&3	0.631
Content of thought	5.9	0.26	6	6	4.6	0.32	4	2	0.005
Disruptive/aggressive behavior	1.9	0.19	2	2	1.5	0.15	2	2	0.115
Appearance	1.7	0.14	2	1	1.8	0.12	2	2	0.818
Insight	3.4	0.09	3	4	3.2	0.10	3	3	0.365

hospitalization). Median of this variable was 1.5 and ranged from 1 to 9 times. Mean and median of number of hospitalization in the Meth- group was 2.3 and 2 times within range of 1 to 8 times. This difference was not statistically significant between the two groups (Mann-Whitney U: $p=0.248$). Mean of duration of the disease (\pm SD) in Meth+ group was 9.1 (\pm 6.5) years (median 8 years; range 1 to 31 years) and in Meth- group it was 9.4 (\pm 8.3) years (median 7 years; range 1 to 30 years) (Mann-Whitney U: $p=0.634$).

Clinical Signs

As shown in Table 2, the mean scale of Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HDRS) and the Scale for Assessment of Positive Symptoms (SAPS) in two groups showed no significant difference.

YMRS

Of the 11 items in YMRS, the two groups

showed no significant differences in 9 items and only in item of speech and content of thought, scores of Meth+ group were significantly higher than the Meth- one (Table 3).

HDRS-17

As seen in Table 4, the two groups were not significantly different in terms of most of the HDRS items, but scores of Meth-patients in work and activity items and scores of Meth+ patients in loss of weight item were significantly higher than the other group.

SAPS

Based on the scale of Assessment of Positive Symptoms (SAPS), in Meth+ group scores of somatic or tactile hallucinations and in Meth- group total score of Global Rating of Severity of Delusions and illogical thinking were significantly higher than their counterparts' (Table 5). Although Meth+ group also scored higher than Meth-

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Table 4. Scores of Hamilton depression scale items (HDRS) in patients with bipolar I disorder with and without methamphetamine use (Meth +, Meth - respectively)

HDRS	Methamphetamine user group (Meth+)				Methamphetamine non-user group (Meth-)				P (Mann-Whitney test)
	Mean	Standard Error	Median	Mode	Mean	Standard Error	Median	Mode	
Depressed mood	0.3	0.07	0.0	0.0	0.2	0.06	0.0	0.0	0.314
Feelings of Guilt	0.2	0.06	0.0	0.0	0.1	0.05	0.0	0.0	0.447
Suicide	0.4	0.11	0.0	0.0	0.3	0.10	0.0	0.0	0.987
Insomnia-early in the night	2.0	0.0	2.0	2.0	2.0	0.0	2.0	2.0	-
Insomnia-middle of the night	2.0	0.0	2.0	2.0	2.0	0.0	2.0	2.0	-
Insomnia-early hours of the morning	2.0	0.0	2.0	2.0	2.0	0.0	2.0	2.0	-
Work & Activities	0.5	0.16	0.0	0.0	1.0	0.22	0.0	0.0	0.025
Retardation	0.1	0.05	0.0	0.0	0.1	0.05	0.0	0.0	0.837
Agitation	0.5	0.11	0.0	0.0	0.6	0.12	0.0	0.0	0.321
Anxiety-Psychic	0.8	0.16	0.0	0.0	1.1	0.18	1.0	0.0	0.135
Anxiety-Somatic	0.7	0.14	0.0	0.0	0.5	1.13	0.0	0.0	0.641
Somatic symptoms-gastrointestinal	0.3	0.07	0.0	0.0	0.2	0.07	0.0	0.0	0.507
General-Somatic symptoms	0.2	0.05	0.0	0.0	0.1	0.04	0.0	0.0	0.264
Genital symptoms	0.4	0.11	0.0	0.0	0.3	0.09	0.0	0.0	0.763
hypochondriasis	0.8	0.19	0.0	0.0	0.6	0.18	0.0	0.0	0.557
loss of Weight	0.8	0.11	1.0	0.0	0.5	0.10	0.0	0.0	0.027
Insight	1.7	0.07	2.0	2.0	1.7	0.07	2.0	2.0	0.744

Table 5. Scores of positive symptoms titles assessment (SAPS) in patients with bipolar I disorder with and without methamphetamine use (Meth +, Meth - respectively)

SAPS	Methamphetamine user group (Meth +)				methamphetamine non-user group (Meth-)				P (Mann-Whitney test)
	Mean	Standard Error	Median	Mode	Mean	Standard Error	Median	Mode	
Auditory hallucinations	2.8	0.18	3	3	2.7	0.18	3	3	0.844
Voices Commenting	1.3	0.14	1	1	1.2	0.14	1	1	0.681
Voices Conversing	1.1	0.13	1	1	1.0	0.16	1	0	0.613
Somatic or Tactile Hallucinations	0.4	0.07	0	0	0.2	0.07	0	0	0.030
Olfactory hallucination	0.1	0.04	0	0	0.2	0.05	0	0	0.582
Visual hallucination	2.3	0.14	2	3	2.0	0.16	2	2	0.095
Global Rating of Severity of Hallucinations	2.5	0.14	3	3	2.3	0.16	2	2	0.350
Persecutory delusions	2.2	0.14	2	2	2.3	0.19	2	2	0.536
Delusions of Jealousy	0.8	0.15	0	0	0.7	0.17	0	0	0.727
Delusions of Sin or Guilt	0.3	0.07	0	0	0.2	0.07	0	0	0.072
Grandiose delusions	3.4	0.15	4	4	3.3	0.19	4	4	0.918
Religious delusions	3.1	0.15	3	3	2.9	0.19	3	3	0.250
Somatic delusions	0.5	0.11	0	0	0.5	0.09	0	0	0.866
Ideas and Delusions of Reference	2.4	0.12	2	3	2.3	0.15	2	2	0.411
Delusions of being controlled	0.6	0.11	0	0	0.5	0.12	0	0	0.354
Delusions of mind reading	0.4	0.10	0	0	0.3	0.08	0	0	0.900
Thought Broadcasting	0.4	0.09	0	0	0.3	0.09	0	0	0.449

in visual hallucinations, delusions of guilt and incoherence, but this difference was statistically only tending to be significant ($0.05 < p < 0.10$).

Table 5. Cntd

Thought Insertion	0.3	0.11	0	0	0.1	0.03	0	0	0.153
Thought Withdrawal	0.2	0.07	0	0	0.1	0.03	0	0	0.107
Global Rating of Severity of Delusions	2.3	0.14	2	2	2.7	0.14	3	2	0.029
Clothing and appearance	1.8	0.14	2	2	1.6	0.16	1	1	0.369
Social and sexual behavior	1.4	0.14	1	1	1.1	0.15	1	1	0.159
Aggressive & Agitated Behavior	2.7	0.17	3	4	2.6	0.15	2.5	2	0.769
Repetitive or Stereotyped Behavior	0.7	0.10	1	1	0.5	0.10	0	0	0.140
Global Rating of Severity of Bizarre Behavior	1.7	0.12	2	2	1.6	0.13	2	2	0.567
Derailment (Loose Associations)	1.5	0.18	1	3	1.4	0.19	1	0	0.556
Tangentiality	0.9	0.13	1	0	1.0	0.17	1	1	0.767
Incoherence	0.5	0.10	0	0	0.3	0.13	0	0	0.093
Illogicality	2.0	0.12	2	2	2.3	0.16	2	3	0.049
Circumstantiality	1.1	0.13	1	2	1.0	0.15	1	0	0.566
Pressure of Speech	3.0	0.16	3	3	3.0	0.16	3	4	0.984
Distractible Speech	2.3	0.15	3	3	2.5	0.17	3	3	0.395
Clanging	0.6	0.10	0	0	0.7	0.13	0	0	0.831
Global Rating of Positive Formal Thought Disorder	2.4	0.11	2	2	2.3	0.14	2	3	0.900
Inappropriate Affect	0.2	0.05	0	0	2	0.06	0	0	0.548

Discussion

To the best of our knowledge, a significant part of the literature has been devoted to studies on association of substance abuse other than methamphetamine (11,12,22), mostly alcohol and mixed drug consumption with demographics and clinical profile of bipolar disorder. Additionally, among several studies about stimulants, including methamphetamine abuse and dependence (7-9), however, few of them evaluated impact of methamphetamine use on clinical presentation of bipolar I disorder. The present study is the first one evaluating role of methamphetamine use on bipolar I disorder symptomatology domain.

In this study, the scores related to somatic or tactile and visual hallucinations in the Meth+ group were significantly higher. In previous studies it has been also demonstrated that presence of any visual or tactile hallucinations in an acute psychosis suggest a psychotic disorder caused by a stimulant or methamphetamine rather than recurrence of a primary psychotic disorder (23,24). Therefore, in cases with acute affective and psychotic symptoms, tactile and visual hallucinations may indicate a probable methamphetamine use disorder.

In a study on patients with diagnoses related to methamphetamine use in a psychiatric emergency setting, most of the pa-

tients in methamphetamine use group were men (70% vs. 57%) and they reported suicide plan (47% vs. 32%) and restlessness (48% vs. 30%) comparing to other psychiatric disorders (25). Correspondingly, in the present study, men were significantly higher than women in Meth+ group. Nonetheless, regarding the presence of suicidal ideation and restlessness, there was no significant difference between the two groups. The reason for this difference may be due to a variety of psychiatric diagnoses such as depression and anxiety in the first study, while patients in the current study were matched for psychiatric disorders except for methamphetamine use.

Comparing the results of both SAPS and YMRS questionnaire indicate that problems in the item of speech in the YMRS in Meth+ group is significantly more severe than the Meth- group. Also, the score of the item of incoherence in Meth+ group of the SAPS questionnaire tended to be partially statistically significant. Both results suggest that thought disorder may be more prominent in patients with methamphetamine use.

Score of the content of thought scale in YMRS questionnaire was significantly higher among Meth+ group comparing to Meth- ones. Although two groups had no significant differences in terms of the score of all types of delusions in SAPS question-

naire, the mean score of most delusions in Meth+ group were higher than Meth-, which is consistent with more severity of content of thought disorder in Meth+ group on YMRS questionnaire.

Significantly higher score of the scale of Global Rating of Severity of Delusions from SAPS in Meth- group might seem incompatible to higher mean scores of all types of delusions in the same questionnaire and higher score for content of thought disorder in YMRS in Meth+ group. However, according to the definition of the SAPS questionnaire, the scale of Global Rating of Severity of Delusions is associated with duration and persistence of delusions, the extent of the subject's preoccupation with the delusions, his/her degree of conviction, and their effect on his/her actions. Therefore, one may conclude that perhaps patients with recurrent episodes of mania without using methamphetamine spend a longer period of time with their delusions before their admission to the hospital. Therefore the extent of the subject's preoccupation with the delusions, the degree of conviction, and their impact on the subject's performance are more severe.

Conclusion

To sum up, the general clinical features of bipolar I disorder in patients who have concurrently used methamphetamine, does not present any significant difference in comparison to bipolar I disorder patients without methamphetamine use. However, in some symptomatology domains, there might be some differences between the two groups.

Limitations

One of the limitations of this study was its small sample size. Given the fact that the higher scores of hallucinations, delusions of guilt, and irrelevant answers in Meth+ compared to Meth- ones tended to be marginally significant, it is possible that in studies with larger sample size one would find significant associations.

The heterogeneous distribution of female and male participants in two groups prevents from generalizing the data to female patients.

Another limitation was difficulty in differentiating mood related symptoms due to mania or methamphetamine intoxication despite follow-up of patients during hospitalization, the rate of symptoms remission and response to treatment.

The other limitation of the current study was the possibility of missing some cases with bipolar I disorders and methamphetamine use which makes our result less generalizable. Considering the fact that we only recruited participants who were diagnosed with bipolar I disorder within 48 hours of their admission to avoid the medication influence on their symptoms we may have missed cases patients were diagnosed afterwards. We also excluded cases with mismatched self-inquiry/meth use tests to avoid over diagnosis of substance use therefore it is possible that we have missed some cases with actual methamphetamine use. Future studies with larger sample size may compensate this limitation.

Moreover, examining variables such as the duration, amount, and route of methamphetamine use, bipolar disorder medications taken before admission, psychotic symptoms in intervals with remission and the main symptoms leading to hospitalization, can provide us with more accurate interpretations about clinical profile of bipolar I patients with and without amphetamine use in the future studies.

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