



Full length article

Does abstinence resolve poor sleep quality in former methamphetamine dependents?[☆]



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ABSTRACT

Background and objective: Among substances that have a significant effect on sleep are stimulants, including amphetamines. As there are few studies assessing sleep quality in methamphetamine withdrawal this study aims to evaluate changes in sleep quality of methamphetamine dependent patients during early remission period by controlling depression and anxiety as confounding variables.

Methods: This study was conducted in Mashhad, Iran. Ninety amphetamine dependent patients, who were admitted in residential centers during 2012–2014 and met our inclusion criteria, were chosen by purposive nonprobability sampling method. Sleep quality was assessed by Pittsburg sleep questionnaire, in the first, second, and after the fourth week of abstinence. Additionally all participants were assessed by Beck Depression Inventory-2 and Beck Anxiety Inventory for controlling depressive and anxiety symptoms.

Results: The prevalence of improper quality of sleep was very high (97.8%) within the first week of withdrawal, but it reduced considerably four weeks after abstinence (52.2%), which was statistically significant ($P=0.00$). The variations of depression and anxiety levels within four weeks after quitting methamphetamine, have low impact on variation of patients' sleep quality (adjusted $R^2 < 0.5$). Furthermore, the effectiveness of these two intervening variables on patients' quality of sleep was dwindled over time after abstinence.

Conclusions: This study showed that the patients' quality of sleep improved significantly four weeks after abstinence and its variation was independent from variations in anxiety and depressive symptoms.

1. Introduction

Sleep disorders have a significant role in the general and clinical health of the society [1]. They could be an independent clinical disorder or a symptom of a clinical syndrome. They usually have direct and indirect effects on the daily functioning and quality of life of sufferer and could lead to significant healthcare costs for the society [2–5]. Each year they affect many individuals and cause intrapersonal and interpersonal impairments [6]. To date, many studies have focused to find out probable etiologies of sleep disturbances and they have shown us the significant correlation between sleep disorders and substance use [7–9]. Among the substances which have a significant effect on the sleep condition are stimulants, including amphetamines [10]. Amphetamines are used for curbing the appetite, increasing attention and concentration, increasing energy and also as an illicit recreational substance [11,12].

It seems that the effect of stimulants on the sleep-wake cycle is fully discussed in the literature. However, our knowledge has mainly derived from the studies performed on the stimulant medications (e.g. methyl-

phenidate) or cocaine; and what is said about the effects of amphetamines on sleep-wake cycle is basically generalization of the results of studies which have been done on the other drugs [13]. Nevertheless there are several reasons that amphetamine and amphetamine-like drugs, especially methamphetamine, have differently influenced the consumers. Amphetamines are known to have longer half-life (9–15 h) in comparison to other stimulants [14]. They have proven neurotoxic effects through reactive oxygen species and hyperthermia, causing axonal injury, especially in synaptic terminals [15,16]. They also lead to significant changes in neurotransmission of glutamate, dopamine, serotonin and norepinephrine causing major behavioral changes [17–20]. Therefore, independent assessment of neurological and psychological alteration of brain activity in methamphetamine abusers is warranted.

According to few researches to reveal the effects of amphetamines on sleep-wake cycle, it has been suggested that consuming amphetamines usually leads to insomnia immediately after usage [10]. It can also lead to hypersomnia in the early withdrawal states [21]. In 1960s Rechtschaffen et al. showed that a small amount of amphetamine can

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increase sleep latency and decrease REM sleep [22]. Withdrawal from amphetamine, on the other hand, can lead to increased REM sleep, lasting for several days [23]. Later in 1990s, Mitler et al. reported same results and showed that methamphetamine can decrease sleep efficiency in low doses (10 mg) [24], although sleep increases for 3–5 days after withdrawal [23]. But other studies brought us more confusing findings. There are also reports of delayed insomnia in users attempting to quit long-term amphetamine use after the 3–5 initial days [23]. Furthermore, the impact of anxiety and depression on sleep quality is not negligible. Stimulants often accompany with anxiety states short after consuming and depressive states in long term use, while patients usually develop depressive symptoms short after quitting them [25]. According to frequent reports, depression and anxiety could have deteriorating effects on sleep quality [26,27]. Therefore, sleep quality of patients who stop using methamphetamines, simply could influence by changes in perceived anxiety or depression. Unfortunately there have not been adequate studies on sleep disorders in amphetamine users.

Considering the importance of sleep health, many studies have examined sleep quality as a marker of general health [28]. Sleep quality, which is a self evaluation of sleep, is considered more important than sleep quantity in the assessment of general health [29,30]. Poor sleep quality is associated with fatigue and impaired mental and occupational functions [31]. This index is affected by many sleep-wake cycle disorders and studies have shown that stimulants affect sleep quality as well [32]. As there are not enough studies assessing sleep quality in methamphetamine dependent patients during prolonged abstinence, especially after prolonged use [33]; the present study aims to evaluate subjective changes in sleep quality of methamphetamine dependent patients during early remission period.

2. Methods

2.1. Subjects

The present study was designed in cross-sectional fashion and was performed in Mashhad City during 2012–2014. Mashhad is the second largest city in Iran, with a population of more than three million people. According to national strategies for treatment of substance use disorder in Iran, there are some residential centers for the treatment of substance use disorders which admit volunteers for almost 3 months. Although individual or group supportive psychotherapies and over-the-counter (OTC) medications are offered in these residential centers, patients have no access to any kind of substances and relapse is prevented in the initial phases of withdrawal, when craving is at its highest. Therefore, patients experience abstinence in these controlled environments during institutionalization. Since there is no psychiatric medication in these residential programs, patients with significant mood and anxiety symptoms, ideas of harm to self or others, intoxication, and psychotic disorders are not allowed to be admitted and are referred to other type of outpatient or inpatient treatment centers. As there is no need for specific pharmacotherapy in the treatment of amphetamine dependence disorder [14], these centers present an opportunity for researchers to evaluate patients, who do not require any kind of pharmacotherapy, for long periods after reaching abstinence. This study was performed in collaboration of participants of these residential centers in Mashhad.

2.2. Procedure

After explaining the project to patients at the beginning of admission to the residential centers, every patient who consented to participate in the study, went through a psychiatric interview to be assessed for the inclusion criteria. Then sleep quality was assessed by Pittsburgh Sleep Quality Index (PSQI). According to McGregor et al. the methamphetamine withdrawal time-course could be divided into acute

(first 7–10 days) and sub-acute (11th–21st days) phases [34]; so, the initial assessment of sleep quality was done in the first week of initiation of withdrawal (before day 3) to rate sleep quality in the acute phase, the second assessment was done in the second week (days 11–14) to rate sleep quality in the sub-acute phase, and the last assessment was done after the 4th week (days 28–35) of abstinence, to rate sleep quality in the primary remission period (according to DSM-IV-TR criteria).

Participants of the study were screened by two trained interviewers (a psychiatrist and a psychologist) by means of structural interviewing. The inclusion criteria was age between 18 and 60 years-old, normal IQ (over 100), methamphetamine dependence disorder according to DSM-IV-TR criteria, no comorbid dependence on other substances except nicotine (occasional abuse of alcohol, opioids, benzodiazepines, cannabis to the extent not warranting a diagnosis of dependency according to DSM-IV-TR was acceptable), not taking medications affecting sleep-wake cycle (in this study, antihistamines among OTCs), no methamphetamine induced disorder other than sleep disorder, no comorbid axis I psychiatric disorder (unrelated to methamphetamine use), and no medical condition affecting sleep. Every patient who fulfilled the inclusion criteria and accepted the written informed consent could participate in the study, so the sampling method was purposive nonprobability sampling. Participants opting to quit the study or the ones discharged before the third assessment were excluded from the study. Sampling was started from March 2012 to August 2014. During this period of time, ninety patients completed the study. Considering the high comorbidity of depressive and anxiety symptoms with sleep disorders [35,36], probable high rates of depressive and anxiety symptoms in the first days of joining to any residential program and also the high frequency of these symptoms in the initial phase of withdrawal from stimulants [34], all participants were given Beck Depression Inventory II (BDI-II) and Beck Anxiety Inventory (BAI) in addition to PSQI for controlling the anxiety and depressive symptoms as confounding variables. All questionnaires were anonymous to prevent any disclosure of personal information and participants were identified with an anonymous number assigned to their profile.

2.3. Instruments

The questionnaires used in this study were:

2.3.1. Pittsburgh Sleep Quality Index (PSQI)

Sleep quality is affected by several factors, and these factors significantly differ in different individuals. Therefore, it seems that a self-report questionnaire is best fitted to assess sleep disorders [3,37]. The PSQI has 7 components and the sum of their scores make the global PSQI score. The participant score the questionnaire on a likert scale from 0 (best condition) to 3 (worst condition), so the minimum score is 0 and the maximum is 21. A global PSQI score over 5 is associated with poor sleep quality. This questionnaire has been studied in various populations and its score is moderately to highly correlate with the sleep quality reported by the patients [38–41].

2.3.2. Beck Depression Inventory-II (BDI-II)

This is a self-report 21-item questionnaire which assesses depressive symptoms. The total score range is from 0 to 63, the higher scores representing a more severe depression. This questionnaire has a high validity in all populations and in depressed and non-depressed individuals which has been reported 0.70–0.90 in different studies [42,43].

2.3.3. Beck Anxiety Inventory (BAI)

Beck Anxiety Inventory is a 21-item questionnaire, assessing the anxiety state of individuals. The total scores range from 0 to 63, higher scores indicating a more severe anxiety. The validity of this scale has

Table 1
Demographic variables and PSQI scores of the participants of the study.

Variable		Frequency
Age (years)		32.1 ± 6.9
Gender (individuals)	Male	74
	Female	16
Marital status (individuals)	Single	29
	Married	43
	Divorced	18
Occupation (individuals)	Unemployed	28
	Employed	62
Quality of sleep in the beginning of study (individuals)	PSQI > 5	88
	PSQI ≤ 5	2
Quality of sleep at the end of study (individuals)	PSQI > 5	47
	PSQI ≤ 5	43

been verified in several studies [44,45].

2.4. Statistical analysis

After data collection, it was analyzed with SPSS software version 11.5. First the distribution of results was assessed by Kolmogorov–Smirnov test. As none of sleep quality, anxiety and depression of participants had normal distribution, we used Wilcoxon signed-rank test to compare the distributions of variables through consecutive assessments. Also we need to estimate the predictive value of variations in anxiety and depression as independent variables on the variation in sleep quality of participants as dependent variable; so, we used general linear regression model and entered variation in both depression and anxiety of participants in a single step analysis to predict the variation in the sleep quality (enter method).

3. Results

In this study, a total of 90 patients with methamphetamine dependence disorder were examined in terms of quality of sleep and symptoms of depression and anxiety through three consecutive measurements. Table 1 summarizes the patients' demographic variables. As shown in Table 1 most of the participants were males, who were married and employed. Preferred route of using was smoking methamphetamine with pipe in all participants. The improper quality of sleep, which is shown with PSQI > 5, was very common within the first days of withdrawal from methamphetamine (97.8% of participants in the first assessment), while its frequency was reduced considerably four weeks after being abstinent (52.2% of participants in the third assessment) (Table 1).

Figs. 1–3 are the scatter diagrams that show the sleep quality

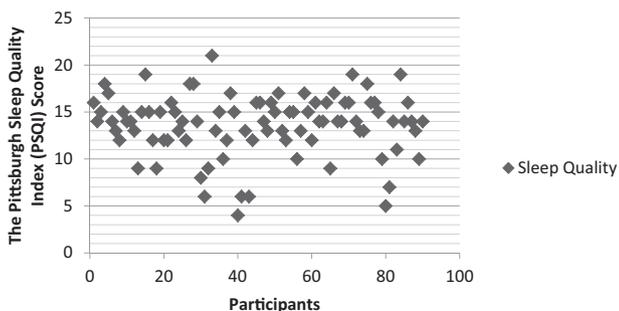


Fig. 1. Pattern of frequency distribution for the sleep quality of participants at days 1–3 of the study (first assessment).

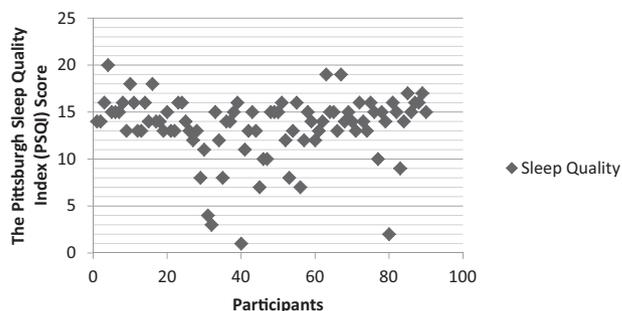


Fig. 2. Pattern of frequency distribution for the sleep quality of participants at days 11–14 of the study (second assessment).

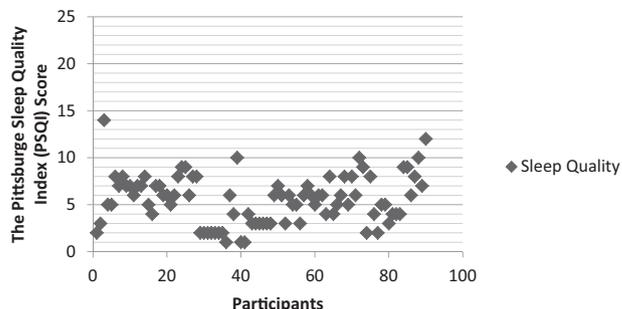


Fig. 3. Pattern of frequency distribution for the sleep quality of participants at days 28–35 of the study (third assessment).

results obtained through three assessments in the participants. According to the diagrams, distribution pattern of sleep quality index of the participants shows minimal changes between the first and second evaluations (Figs. 1 and 2), but it appears that the last assessment which was done one month after quitting the substance has different pattern of distribution (Fig. 3). Given the results of the Table 2, mean sleep quality scores of the participants has reduced significantly in the third assessment in comparison to the previous assessments (P=0).

Table 3 shows the mean changes of the sleep quality, depression and anxiety of the participants through the three consecutive measurements. The data indicates that the index of sleep quality of participants has considerable reduction four weeks after the complete abstinence from methamphetamine, yet the scores of BDI-II and BAI decreased in repeated assessments too. Considering the fact that the alteration in depression and anxiety symptoms can influence the patients' quality of sleep, the multivariate regression model was used to measure the impact of the decreased scores of patients' depression and anxiety on the decreased index of sleep quality. Table 3 shows the respective results. Although the variations of depression and anxiety levels within four weeks after stopping amphetamine use was significantly effective in prediction of patients' variation of sleep quality, the measured impact was low (adjusted R² < 0.5). Furthermore, the impact of these two intervening variables on patients' quality of sleep was dwindled over time after quitting amphetamine use (Table 4).

Table 2
Comparison of the quality of sleep of participants between three stages of the study.

Variable		Z	P
Quality of sleep	Comparison between the first and second measurement	0.48	0.63
	Comparison between the first and third measurement	8.25	0.00
	Comparison between the second and third measurement	8.20	0.00

*using Wilcoxon signed-rank test

Table 3
Quality of sleep, depression and anxiety of the participants at three stages of the study.

Variable	Timing of Evaluation		
	First Assessment (days 1–5)	Second Assessment (days 11–14)	Third Assessment (days 28–35)
Quality of sleep	13.6 ± 3.3	13.5 ± 3.4	5.5 ± 2.6
Depression	31.8 ± 10.4	28.5 ± 10.5	19.9 ± 9.1
Anxiety	26.7 ± 4.4	25.2 ± 12.2	15.5 ± 8.3

4. Discussion

In this study the prevalence of improper sleep quality was reported 97.8% and 52.2% within days 1–5 and by the end of fourth week (days 28–35) of abstinence from methamphetamine, respectively. Repeated measurements of patients' depression and anxiety levels indicated that the improved depression and anxiety levels in patients, within four weeks after quitting methamphetamine use, can totally predict 15% of the improved sleep quality in patients. In other words, 85% of the reported improvement which happened within four weeks after total abstinence can be attributed to stopping use of methamphetamine, itself.

Results showed that the improper quality of sleep during the early days of treatment was reported very high (97.8%). Since the quality of sleep, which is measured by PSQI, is the outcome of several parameters including the general description of the subject on his/her own sleeping, the sleep latency, sleep duration, sleep sufficiency, sleep maintenance and morning performance, any change in the mentioned factors may decrease sleep quality [41]. There are reports about the reduced sleep duration, the prolonged delay in falling sleep, decreased sleep duration and more frequent spontaneous awakenings from sleep within 3–5 days after using amphetamines [13]. On the other hand, it has been suggested that quitting methamphetamine use may increase the daytime drowsiness [28]. Therefore, the low quality of sleep due to using methamphetamines is expected. However, the high prevalence of disturbed sleep in the early days of study demonstrates that methamphetamines broadly affect the brain centers which are tasked with regulating the sleep-wake cycle. In fact, 88 out of 90 participants reported the low-quality sleep at the beginning of the study; while analysis of low-quality sleep prevalence in other chronic diseases using similar tool (PSQI) showed lower values. For instance, studies have shown that sleep quality is usually low in 75% of patients with end-stage renal disease who are being treated with dialysis [46], 56% of patients suffering systemic lupus erythematosus [47], 47% of patients with Parkinson disease [48] and 71% of patients with type 2 diabetes mellitus [49]. Thus, the very high prevalence of low-quality sleep in methamphetamines users emphasizes the importance of sleep problems issues in treatment protocols. On the other hand, although the drug tolerance is common after long-term use of most stimulants, the high rate of sleep disturbance at the beginning of this study indicated that tolerance to the disturbing effects of methamphetamine on sleep-wake cycle is not observed in methamphetamines abusers, even in severe cases such as methamphetamine dependence disorder patients.

Table 4
Multivariate regression model of impact of Variation in depression and anxiety on the Variation in sleep quality of participants of the study.

Timing of evaluation	Major variable	Intervening variable	B	β	95% Confidence Interval for B		R	Adjusted R ²	P
					Lower bound	Upper bound			
Third evaluation compared to the second evaluation	Variation of sleep quality	Variation of depression	0.11	0.23	0.02	0.24	0.57	0.31	0.00
		Variation of anxiety	0.17	0.44	0.10	0.21			
Third evaluation compared to the first evaluation	Variation of sleep quality	Variation of depression	0.07	0.22	0.00	0.13	0.41	0.15	0.00
		Variation of anxiety	0.07	0.27	0.02	0.13			

Given the Figs. 1–3 and Table 2, it was found that the quality of sleep did not change considerably within the subacute phase of amphetamine withdrawal syndrome rather the early days of the treatment. McGregor et al. pointed that the subacute phase of methamphetamine withdrawal syndrome is characterized by the slighter symptoms of the acute phase syndrome [34]. But in the present study, sleep disturbances remained in subacute phase and no improvement was observed between the first and second evaluation of sleep quality (P=0.63). Even it seems that some patients have experienced worse sleep quality in subacute phase of withdrawal that the acute phase, therefore in patients with methamphetamine dependence disorder, even fourteen-day duration after the last use of the drug is not sufficient for restoring the neurobiological damages in brain centers regulating the sleep-wake cycle and the patients could not clinically feel any improvement in their quality of sleep. Thus, it can be concluded that the neuronal damage is intensive and the recovery phase is slow for those who suffer from methamphetamine-induced sleep disorders. It is noteworthy that due to polysomnography protocols it is recommended that the patients with the background of stimulant use should stop using the drug at least for one week before polysomnography. Based on the given results, it seems that polysomnographic evaluation for the methamphetamine users should not be conducted even in the second week of abstinence. Also, the positive correlation between sleep disorders and craving in patients with methamphetamine dependency demonstrates the importance of managing patients' sleep problems during either acute or subacute phases of the treatment.

Results showed that more than half of the participants still suffered from the severe disturbances in their sleep even in the fifth week after reaching abstinence from amphetamines and amphetamine-like derivatives. This finding does not support the results observed after prescribing amphetamines for the rhesus macaque. In a study conducted on methamphetamine self-administration in the rhesus macaque, Anderson et al. showed that the quality of sleep will be normal again immediately after stopping methamphetamine prescription [7]. A disturbed sleeping condition lingering for more than a month after quitting methamphetamine showed that in methamphetamine dependents, behavioral symptoms attributed to withdrawal from methamphetamine are not simply an opposite form of behavioral symptoms which are present in the course of using these drugs. This can support the hypothesis that the neurobiological pathways affecting by using drugs, which are in charge of the behavioral phenomena of substance use disorders, are separated from those affecting during withdrawal syndromes. It seems that a kind of adaptation is developed in sleep-wake cycle-related systems in brain during abusing amphetamine and amphetamine-like substances, so withdrawal from methamphetamine is not simply an opposite form of using it. According to some studies, this adaptation is caused by the formation of a secondary pacemaker as an opponent process to regulate sleep-wake cycle out of the suprachiasmatic nucleus. As a result, quitting amphetamines, while activation of the opponent processes remained in this system, results in some more durable symptoms in patients' sleep-wake cycle [13].

Present study showed that the patients' quality of sleep variation was independent from the patients' affective symptoms. These affective symptoms could be generated in the patients of residential centers,

because of a maladaptive reaction to a strange and not familiar environment which staying at, because of the natural course of abstinence of any drugs which affect the reward pathway and stress axis of the human brain or because of stopping any beloved and habitual behavior. Within five weeks of this study, not only the quality of sleep was improved, but also the severity of depression and anxiety reported by patients was reduced. The results demonstrated that only 15% of the recovery occurred in patients' sleep quality can be attributed to their reduced depression and anxiety symptoms within the first four weeks of quitting methamphetamine (Table 4). Regarding this fact that the current data are not sufficient to understand how amphetamine users' sleep pattern changes, the above finding seems to be the most important finding of the present study. The independent recovery of sleep quality in methamphetamine users not only highlights the independent neurobiological damages caused across the brain circuits linked to sleeping process, but also revives hopes to treat the sleep disorders in patients with amphetamine dependency. Although more than half of the participants still suffered from sleep disorders within the fifth week after quitting amphetamines, it must be considered that their sleep quality was improved significantly ($P=0.00$). Since we used the cut-off score of 5 for PSQI, the eight-score reduction in the average score of patients' sleep quality (according to Tables 2, 13.6 ± 3.3 change into 5.5 ± 2.6 , which is close to the cut point of 5), can support a good prognosis for amphetamine-induced sleep disorder. However, the amphetamine addicts need to be warned about the long period of time needed to reach full recovery.

This study is important as it tried to measure the sleep quality (through consecutive measurements) by simultaneously controlling the intervening variables (suffering from medical disorders, psychological disorders, abusing other substances, using psychotherapeutic medications, lapse and relapse) during study. In fact, most patients with amphetamine dependence disorders suffer from poly substance dependence disorder as well. Hence, separating the effects of each substance on sleep-wake cycle which was done in the present study is very difficult. Also, the high prevalence of comorbidity of amphetamine dependency with aggression, paranoia, and psychosis [14] often necessitates prescription of tranquilizers for patients, which affect the sleep-wake cycle [50]. So studying a pure group of methamphetamine dependents with no psychiatric comorbidity, which was done in the present study, may provide promising and valuable data for the researchers. Moreover, finding patients who can resist against the craving for stimulants for four weeks and also agree to cooperate with psychological assessments is another obstacle which was overcome in our research.

5. Limitations

This study has its limitations. Lots of patients participated in this study were male. They were severely affected by methamphetamine which they prefer to be institutionalized to reach abstinence. Moreover, the characteristics of the drug used by patients such as dose and duration of abuse were not addressed. It was due to the unreliable reports of participants with methamphetamine dependency in terms of the precise dose and duration, unreliable purity of the illegal drugs they use, irregular pattern of weekly use (for example times of use could change from week to week for an individual) and gradual tolerance to amphetamines which could attenuate the physiological effects of the specific amount of the drug in consumers [10] and reduce correlation between the characteristic of methamphetamine induced sleep disorders and the amount of methamphetamine which is used.

Given the significant improvement in patients' sleep quality within four weeks of abstaining from using methamphetamines, it would be better to conduct longer follow-up periods. Therefore, considering longer follow-up courses alongside applying more objective analysis tools for sleep disorders (e.g. polysomnographic studies) in designing future surveys, are suggested.

Conflict of interest

We declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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