

## Comparison of Sleep Problems in Opioid-Dependent Patients under Methadone and Buprenorphine Treatment

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### Abstract

**Background and Objective:** The main aim of the current research was to compare sleep problems in two groups of patients with addiction treated with preservatives substances (i.e., methadone and buprenorphine).

**Materials and Methods:** Two groups of addicts (30 patients treated with methadone and 30 patients treated with buprenorphine) were voluntarily selected using an available sampling method and were asked to complete Pittsburgh sleep quality index (PSQI), Epworth sleepiness scale (ESS), Insomnia Severity Index (ISI), and STOP-BANG questionnaires. Data analysis was performed using independent t-test and descriptive indicators at the significant level of 5%.

**Results:** The average age was  $39.16 \pm 5.07$  in the methadone group and  $40.30 \pm 6.17$  years in the buprenorphine group ( $P < 0.050$ ). All participants were male. Current findings indicated that significant difference existed between the two studied groups in the PSQI ( $P < 0.001$ ) and ESS ( $P < 0.010$ ) with the higher mean score for the methadone group. However, buprenorphine group showed higher mean score than methadone group on the ISI and STOP-BANG and these differences were found statistically significant ( $P < 0.010$ ).

**Conclusion:** Sleep problems may be one of the reasons for the failure in the treatment of addiction among patients with addiction.

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**Keywords:** Addiction; Methadone; Buprenorphine; Sleep

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### Introduction

The most, worldwide, a common treatment for people with opioid abuse is opiate substitution therapy, also known as maintenance therapy. At present, the two major types of drugs used in the maintenance therapy are methadone and buprenorphine (1). Methadone is an artificial opiate substance and a  $\mu$ -opioid agonist, and a daily oral dose can prevent the onset of withdrawal symptoms up to 24 hours or more. The normal dose at the outset of treatment is usually 15-30 mg (2). Similar to methadone, the maximum effect of buprenorphine is less than opioids such as heroin and methadone, despite the fact that it is classified as opioids with their specific complications, such

as euphoria and impaired respiratory system; the optimum therapeutic effect of buprenorphine is in the range of 16-32 mg (3). The bulk of studies on the effectiveness of maintenance therapy on various aspects of health suggest that maintenance therapy with methadone and buprenorphine, despite its positive effects on discontinuation or reduction of one's craving for drugs and consequently lowers chance of relapse, has some negative side effects including sleep problems (4).

Sleep abnormalities as the side effects of substance abuse are generally associated with daily drowsiness, which can affect mood, alertness, memory, security, and function of an individual (5). The results of some studies have shown that damages caused by the use of methadone and buprenorphine can disturb the state of sleep and daily activities and also affect other aspects of life, participation in the treatment and its continuation (6).

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Accordingly, a number of studies have shown that maintenance therapy may be associated with some types of sleep disorders (7). In a study by Speed et al. on addicts treated with buprenorphine, participants were subjected to electroencephalogram records for 1 week, and indices of the duration of sleep, wake-up after sleep, low sleep quality, and delayed sleep phase were investigated. The results suggested that although buprenorphine triggered sleep disturbance, it induced significantly longer and higher sleep quality compared to the other drugs used for the treatment of addiction (8). In the same vein, a clinical study by Lukas et al. (9) revealed that buprenorphine improved sleep structural abnormality to a desirable level. Significant sleep changes induced by addiction appeared after the administration of low doses (rather than high doses) of buprenorphine. However, some studies suggest a positive relationship between sleep problems and use of buprenorphine. For instance, the study of Gauthier et al. demonstrated that buprenorphine could cause sleep disturbance despite its analgesic effects in treating addiction (10). However, a number of studies such as the one conducted by Fischer et al. pointed to the greater therapeutic effect of methadone compared to buprenorphine (11). In this context, Sharkey et al. compared the state of sleep problems in 62 methadone-treated patients using polysomnography (PSG) by monitoring the sleeping state of 62 methadone users for 1 week. The results suggested that factors of mean sleep, subjective satisfaction with sleep, relaxation, and sleep efficiency in PSG were significantly correlated with Pittsburgh sleep quality index (PSQI) scores (12). The results of this study illustrated that use of methadone in the treatment of addiction caused sleep disturbance, but simultaneous use of benzodiazepine medications could help reduce sleep problems and treatment process. Few studies have explored the effects of methadone and buprenorphine on sleep problems, especially in Iran. However, given complications associated with the use of maintenance therapy, as shown in several studies, it is still unclear which of these drugs may play a more effective role in the treatment of addiction with fewer side effects on sleep. The aim of this study was to investigate sleep problems in patients with opioid addiction treated with methadone and buprenorphine replacement therapy.

## Materials and Methods

The study population consisted of all patients

with opioid addiction in Mashhad City, Khorasan Razavi Province, Iran. This descriptive-comparative research was conducted on people referring to five addiction treatment clinics in Mashhad City in 2016 who were treated with maintenance therapy. At first, consent letter was obtained from the addiction treatment centers. Then, for selecting participants, a list of drug addicts treated with methadone and buprenorphine (those who were treated with either methadone or buprenorphine, based on their medical condition as decided by a physician in charge of the clinic) was prepared. After the initial interview, PSQI was completed for them. Then, from both groups, subjects with a higher, a score of 5 or more, were assigned to have sleep problems, 60 individuals ( $n = 30$ , treated with methadone;  $n = 30$ , treated with buprenorphine), who had the eligibility criteria to participate in the study, were selected. The inclusion criteria were: the lapse of at least 1 year from the start of the treatment (to stabilize the dose), the average dose of methadone (a daily dose of 80-90 mg) and buprenorphine (a daily dose of 14-16 mg), complaining from a sleep problem, no other serious mental disorders or physical illness, being male, age range of 30-50 years, and history of opioid addiction. The exclusion criteria were drug abuse and changes in prescription drug during the study period. Participants were selected using available sampling method. After completing the informed consent form, participants were asked to complete forms including PSQI, Epworth sleepiness scale (ESS), Insomnia Severity Index (ISI), and STOP-BANG. Moreover, the body mass index (BMI) of individuals, as one of the items in STOP-BANG test, was calculated. In this research, descriptive indices such as mean and standard deviation and independent t-test were used to analyze the data. The data analysis was performed by SPSS software (version 16, SPSS Inc., Chicago, IL, USA).

**PSQI:** PSQI is a useful tool designed for assessing sleep quality; this questionnaire was developed in 1989 by Buysse and Colleagues at the Pittsburgh Institute of Psychiatry. It is originally a 9-item questionnaire, but question 5 contains 10 sub-items, so the whole questionnaire consists of 19 multioption items with Likert scale scored from 0 to 3. This questionnaire has seven components including sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disorders, use of sleeping aid drug, and daytime dysfunction. The overall score 5 or above means poor sleep quality.

**Table 1.** Age and body mass index in two different studied groups

Variable	Group	Mean ± SD	Minimum	Maximum
Age (year)	Methadone	39.16 ± 5.07	30	48
	Buprenorphine	40.30 ± 6.17	32	50
BMI (kg/m <sup>2</sup> )	Methadone	26.13 ± 2.25	15.72	38.41
	Buprenorphine	30.25 ± 3.81	16.68	43.57

BMI: Body mass index

The questionnaire has a sensitivity of 0.089 and specificity of 0.086. Number of 5 inpatients compared to control subjects has been reported to be sufficient by the creators of this scale (13).

**ESS:** ESS with eight items was designed to determine the level of daytime sleepiness. All questions are concerned with how likely a person feels sleepy in various situations. The test is a list of eight situations in which person rates his/her tendency to become sleepy on a scale of 0, no chance of dozing, to 3, high chance of dozing. The total score of ESS ranges from zero (impossible to sleep in any position) to 24 (Likely to be sleepy at all 8 items). According to the total score, a participant can be labeled as the following categories: 0-7: abnormal sleepiness is unlikely, 8-9: an average amount of daytime sleepiness, 10-15: excessive sleepiness (likely to need medical attention), and 16-24: excessive sleepiness and needs medical attention. The Cronbach’s alpha for ESS has been reported 0.70 to 0.73 in different studies (14,15).

**ISI:** ISI contains seven questions with a Likert scale response, ranged from zero (no problem) to 4 (severe), and has been designed to evaluate insomnia and its consequences on daily life. The questionnaire score 8 or above indicates insomnia: 0-7 = No clinically significant insomnia, 8-14 = Subthreshold insomnia, 15-21 = Clinical insomnia (moderate severity), and 22-28 = Clinical insomnia (severe). The reliability of the questionnaire has been reported 0.74 by Bastien and Morin (16). The reliability of the ISI questionnaire using internal consistency was reported 0.91 in Morin

et al. (17) study.

**Sleep apnea screening questionnaire (STOP-BANG):** STOP-BANG is a reliable instrument for screening obstructive apnea during sleep. The questionnaire consists of eight items that include snoring, tiredness, observed apnea, use of antihypertensive drugs, a BMI higher than 35, age above 50 years, neck circumference of more than 40 cm, and the male gender. The positive answer to each question is scored 1. Three or more positive responses out of 8 indicate a high risk of obstructive sleep apnea and <3 positive responses indicates a lower risk of obstructive sleep apnea (18). The content validity of this questionnaire was confirmed by Chung, and its reliability was measured by retest (0.96) in test-retest (0.90) methods (19).

**Results**

The mean age of study participants was 39 ± 5.07 years in the methadone group and 40.30 ± 6.17 years in the buprenorphine group (P = 0.035). Sixty seven percent of the participants were married, and all were men. The mean BMI was 30.25 ± 3.81 kg/m<sup>2</sup> in the buprenorphine group and 26.13 ± 2.25 kg/m<sup>2</sup> in the methadone group (Table 1).

Table 2 summarizes some descriptive characteristics of sleep problems for both the groups. Scores between the two groups (methadone and buprenorphine) in terms of sleep quality and sleepiness were higher in the methadone group. The scores of STOP-BANG and ISI were higher in buprenorphine than methadone group.

**Table 2.** Mean, standard deviations, and independent sample t-test in two different studied groups

Variables	Group	Mean	SD	P-value
PSQI	Methadone	12.31	2.07	< 0.001**
	Buprenorphine	8.96	2.80	
ESS	Methadone	9.73	1.63	0.001*
	Buprenorphine	8.13	1.50	
ISI	Methadone	18.93	3.20	0.001*
	Buprenorphine	22.03	2.87	
STOP-BANG	Methadone	1.93	0.82	0.001*
	Buprenorphine	3.20	1.37	

PSQI: Pittsburgh sleep quality index; ESS: Epworth sleepiness scale; ISI: Insomnia Severity Index; STOP-BANG: Sleep apnea questionnaire; \*P < 0.010; \*\*P < 0.001

Furthermore, as table 2 shows, the results of the independent t-test for equality of means showed a significant difference between two studied groups (methadone and buprenorphine) in four compared variables, sleep quality ( $t(58) = 5.18$ ,  $P < 0.001$ ), ESS ( $t(58) = 0.394$ ,  $P = 0.001$ ), ISI ( $t(58) = -3.94$ ,  $P = 0.001$ ), and STOP-BANG ( $t(58) = -4.32$ ,  $P = 0.001$ ).

## Discussion

Based on the findings of this study, buprenorphine users were in a better position in terms of sleep state and sleep quality indices compared to the methadone group. Participants treated with buprenorphine had better sleep quality indices, such as delay in falling sleep, sleep duration, sleep efficiency, and frequent wake-ups. This is consistent with the results of Lukas et al. (9) who indicated that the use of buprenorphine improves structural sleep problems (including delayed sleep phase syndrome, decreased sleep duration, frequent wake-ups after falling sleep, reduction in rapid eye movement onset latency, and a significant reduction in slow-wave sleep) caused by heroin or cocaine. Furthermore, in a relevant research by Speed et al., which measured sleep disturbance in patients treated with buprenorphine by electroencephalography, variables such as sleep duration, sleep deprivation, and delayed sleep phase were investigated. The results suggested that although buprenorphine induced sleep disturbances, it also improved sleep quality and prolonged sleep duration more than other addiction treatment drugs ( $P = 0.090$ ) (8). In line with this study, Sharkey et al. (12) in their study on sleep disturbances of methadone users by PSG, which was significantly correlated with PSQI scores, revealed that the use of methadone for the treatment of addiction would cause sleep problems. Another complication in patients under treatment, especially those who have recently begun treatment, is muscle pains caused by drug discontinuation. The results of the comparison of sleep quality indices, including pain in sleep, suggested that patients using buprenorphine had less pain during sleep. In this regard, Peles et al. (20) in their study on 101 methadone-treated subjects for sleep problems concluded that 46.5% of methadone users had chronic pain during sleep. The average score of PSQI was  $9.0 \pm 4.8$ , with 75.2% of the subjects reporting poor quality sleep. The mean score of PSQI in our study was  $12.5 \pm 10.15$ , which may indicate

poor sleep quality of methadone-treated patients triggered by an experience of pain during sleep.

In this respect, buprenorphine had a stronger therapeutic effect than did methadone. In fact, since buprenorphine has a longer half-life with stronger analgesic effects, it can alleviate the pain of patients coping with drug withdrawal syndromes for a longer period of time and contribute to the deterrence of relapse temptation. For this reason, it significantly leads to longer and higher-quality sleep compared to similar drugs in the treatment of addiction (21).

Present results showed that patients treated with buprenorphine had a higher score in subscales of STOP-BANG such as BMI compared to the methadone group. Furthermore, there was a significant difference in terms of the other subscales of this index such as high blood pressure and snoring. This is in agreement with the results reported by Farney et al. (22) and Gauthier et al. (10). They found that a large portion of patients treated with buprenorphine to have mild sleep apnea. In the same vein, studies of Pjrek et al. (23) reported that patients treated with buprenorphine had less and shorter sleep efficiency than did patients treated with methadone. This can be explained with regard to the fact that insomnia observed in the buprenorphine group could be due to interruptions in breathing and subsequent wake-up, which in turn provokes tiredness during the day, and is probably related to the side effects of buprenorphine. However, as shown by the results of this study and previous studies, while buprenorphine leads to some types of sleep problems such as sleep apnea, it has positive effects such as enhancing the quality and duration of sleep (24). Physical and psychological aspects such as physical health, memory, learning, attention, and executive functions are seriously affected by inadequate or undesirable sleep. In addition, complications such as anxiety, mood disorders, depression or excessive euphoria, delusions, and uncoordinated movements, which are frequently observed in extreme cases of drug dependence, could also be caused or exacerbated by prolonged sleep problems (25).

This study had a number of limitations, including controlling for gender, unavailability of the PSG, drug and dose of usage and age as well as lack of control over HIV status of the patients. In addition, since the research was undertaken in the city of Mashhad, caution should be noticed in the

generalization of the results. Our suggestion for the future research is to study the relationship between sleep problems and severity of drug dependency. Moreover, evaluating participants' sleep by objective diagnostic tools such as actigraphy and PSG is recommended.

## Conclusion

Participants treated with buprenorphine had better sleep quality indices, such as delay in falling sleep, sleep duration, sleep efficiency, and frequent wake-ups compared to the ones used methadone for replacement therapy.

## Conflict of Interests

Authors have no conflict of interests.

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