

Risk of Sleep Apnea in Stable Methadone Maintenance Treatment Patients and Opium-dependent Patients

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Abstract: The aim of the present study was to evaluate the risk of sleep apnea in patients undergoing methadone maintenance treatment and opium dependent patients without treatment. sixty five patients in MMT group and 61 patients in opium dependent group were selected from among the patients undergoing MMT and new patients referring to MMT who have not received treatment. The Berlin questionnaire was used to evaluate the risk of sleep apnea. The results indicated that twenty one patients in MMT group (32.3%) and 24 patients in opium dependent group (36.9%) classified as high risk for sleep apnea. there was no significant statistical difference between the two groups in terms of the risk of sleep apnea ($P\text{ value}=0.41$). we conclude that use of methadone maintenance treatment for quitting opium dependency does not increase the risk of sleep apnea.

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Introduction

Opioid dependency is a chronic and often relapsing disorder with numerous physical and psychological complications, which also can bring about social, economic as well as health problems (1).

It is known that sleep disorders and sleep-disordered breathing (SDB) are problems associated with substance dependency (2, 3). SBD is characterized by repeated pauses in breathing during sleep, which results to the fragmentation of sleep. This condition has spectrum ranges from partial to complete airway collapse and episodes of apnea. Sleep apnea syndrome can be life-threatening and has been associated with stroke and other cardiovascular morbidity and mortality (4). In a retrospective cohort study, Walker and colleagues determined the effect of morphine dose equivalent on breathing patterns during sleep. They found that in patients taking chronic opioids, the apnea-hypopnea index (AHI) is higher than control subjects due to the increase of central sleep apnea (CSA) (5).

Methadone maintenance treatment (MMT) is the selective treatment for quitting opiate substances which reduces mortality, crimes and hazardous behaviors (6).

However, there are a number of studies to assessment the sedative effects of opioids, few studies have investigated the effects of opioids on

sleep architecture, even though opioids have been reported to cause disrupted sleep and abnormal sleep architecture (7-9). Furthermore, previous studies have shown that CSA occurs in approximately 30% of patients on stable MMT (10, 11). Sleep apnea itself can cause significant daytime sleepiness and reduced daytime function (12). However, few studies have investigated the risk of sleep apnea in large sample subjects on stable MMT. Therefore, this study conducted to compare the risk of sleep apnea in patients on stable MMT and those who opium-dependent.

Materials and Methods

This cross sectional study was conducted from September 2010 to December 2011 in Kermanshah University of Medical Sciences (KUMS) after the approval of ethics committee institution of KUMS. We recruited a total number of 311 subjects from patients undergoing methadone Maintenance treatment and opium-dependent individuals who referred to Kermanshah MMT centers. To be eligible for the study, patients on MMT had to be on methadone for 2 months or longer and had to be on a stable dose of methadone. The required sample size is 65 people in each group, given the prevalence rate of sleep disorders in methadone treatment group and the control group (75% and 95% respectively and assuming 90% power

to identify significant statistical difference between the two groups). The value of alpha was assumed 0.05 to calculate the sample size. A screening examination was performed to exclude those subjects with severe cardiac, respiratory, neurological, or liver disease. Patients who had diagnosed psychotic disorders and who use of stimulants and sleep medications were also excluded. Normal control subjects were recruited through advertisements placed on public notice boards with no mention of the research topic.

The patients, who agreed to participate in this study, filled out the Berlin and demographic questionnaires. The Berlin questionnaire consists of three categories designed to illicit information regarding snoring (category 1), daytime somnolence (category 2) and the presence of obesity and/or hypertension (category 3). In categories 1 and 2, patients answering "almost every day" or "3-4 times per week" are considered to have significant symptoms. The presence of obesity (body mass index (BMI) [30 kg/m²]) and/or hypertension in category 3 is considered significant. This questionnaire is developed in 1996 and reliability and validity of its Persian version stated previously in primary care condition (13).

Categorical data were analyzed with Chi-square or Fisher exact test and Student t test for continuous data. $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS version 19.0.

Results

During the study period, three hundred fifty six men that had been referred to the KUMS MMT centers were initially recruited and volunteered to participate in this study. 126 of them met our inclusion/exclusion criteria (65 in MMT group and 61 patients in opium dependent group). Table 1 shows demographic characteristics of the study participants. The subjects of the two groups were matched for duration of drug abuse and body mass index (BMI). However those who were opium dependent were younger than MMT group ($p = 0.009$).

According to the Berlin Questionnaire, from total of 126 participants 27.8% (35 patients) were classified as high risk for apnea. However the distribution of such patients among two groups did not reach to statistical significant level. Twenty one patients in MMT group (32.3%) and 24 patients in opium dependent group (36.9%) classified as high risk for sleep apnea ($p = 0.41$). Using logistic regression analysis and after adjustment for age and group (MMT or opium dependent), BMI increased the risk of apnea (OR=1.16, 95%CI: 1.04-1.30).

Table 2 depicts Berlin Questionnaire findings in these 126 patients.

Discussion

In the present study, we compared the risk of sleep apnea in patients on stable MMT and those who opium-dependent. Although, the treatment with methadone is a clinically effective method for narcotic withdrawal (6), however, problems or unpleasant side effects of using this method require further caution in its use and also need more accurate study about it.

According to the results of the present study, no significant difference was observed between the group treated with methadone and opium dependent group in terms of sleep apnea. In other words, the prevalence of sleep apnea risk in people treated with methadone is not greater than opium-dependents. The results clearly demonstrate the ideal situation of the people treated with methadone compared with opium abusers. Our results showed that patients enrolled in methadone maintenance therapy as well as opium dependent had high risk for sleep apnea. In our sample, 32.3% of MMT patients and 36.9% of opium dependent classified as high risk for sleep apnea. The prevalence of OSA in our sample is higher than observed in the general population (14-16). Given the increased risk of OSA in men, it is notable that male sex may correlate with high presence of risk for sleep apnea in our sample.

One of the most dreaded sleep disorders suspected to be associated with chronic methadone treatment is sleep apnea (10, 11, 17). Previous studies of patients in MMT for opioid dependence have corroborated central sleep apnea (CSA) despite evidence that obstructive apneas and hypopneas are also exist in this population (10, 11).

The results of our study are, to some extent, consistent with previous research. The findings of Walker *et al.* study on the effects of opioids on breathing during sleep, suggested that apnea-hypopnea index in opioids abusers is high due to the increase of central sleep apnea (18). In Sharkey *et al.* study (2010), the prevalence of obstructive sleep apnea in methadone users was 32% (19), which is comparable with the finding of our study specifying 31%. Also, Stein *et al.*, conducted a study on 225 patients undergoing methadone maintenance treatment. Based on the results of their study, 84% of patients treated with methadone had serious sleep problems (20).

Although our study has shown that stable MMT patients do not have significantly different in the risk for obstructive sleep apnea when compared to opium dependent subjects, but some studies showed that the increment found in obstructive sleep

apnea based on apnea-hypopnea index (AHI), is due to CSA in MMT patients. Central apneas occurred more often in non-REM sleep than REM sleep in MMT patients and that obstructive apneas occurred more often in REM sleep than non-REM sleep (11).

Central respiratory depressant effect of methadone may have a critical role for generation of CSA. On the other hand, methadone blood concentration is the most significant predictor of the severity of CSA in MMT patients. Also, brainstem and/or midbrain structural abnormalities could be causing CSA via central controller pathology in MMT patients (11).

Our observation of associations between obstructive sleep apnea and higher BMI are consistent with previous studies (21, 22). It's reported that duration of MMT was related to the presence of OSA. Some patients MMT may lead to weight gain, and that body mass index is, in turn, associated with the development of OSA (19).

Supporting our findings, BMI change and time were significant predictors for AHI change in a study by Young et al, that evaluated untreated patients with primary snoring and obstructive sleep apnea by using polysomnography (23). In addition, obstructive sleep apnea among MMT patients was associated with higher BMI and longer duration in MMT (19).

Increment in weight among MMT patients was reported to be comparable with that of the general population (24). This weight gain may relate to the Reward Deficiency Syndrome (RDS) that characterizes drug addicts (25) before the addiction and that may debase during the chronic substance use and pathologically alters further the reward set point in a manner that may diminish ability to enjoy any other rewards, even the very natural rewards activities such as food and sex (26). Thus, the lifestyle change and stabilization that follows the entrance of opiate addicts into an MMT program lead to a consistent increase in weight (24).

Table 1. Demographic characteristics of the study participants

	MMT group (n=65)	Opium dependent group (n=61)	p value
Age (year)	38.8±11.1	34 ±9.2	0.009
Body Mass Index (kg/m ²)	25.2±4.1	23.9±3.2	0.05
Duration of use (year)	9.9±7	9.7±7.4	0.935

Table 2. Berlin Questionnaire findings of the study participants

	MMT group (n=65)	Opium dependent group (n=61)	p value
Category 1, n (%)	14	18	0.304
Category 2, n (%)	25	37	0.013
Category 3, n (%)	11	3	0.032
High risk for OSA, n (%)	21 (32.3)	24 (36.9)	0.41

Conclusion

According to the present study, use of methadone maintenance treatment is not associated with an increased risk of sleep apnea. Although sleep problems have been reported in 75 to 84 percent of people using the MMT (20, 27, 28) and sleep apnea disorder is common among these patients (10, 11), it seems that there is no concern for using methadone maintenance treatment for quitting opiate. However, it is necessary to pay more attention to sleep problems in both groups.

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