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Higher Risk for Obstructive Sleep Apnea in Chronic Treatment-Resistant Depression

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Abstract

Background: Studies reported the strong link between Obstructive Sleep Apnea (OSA) and Major Depressive Disorder (MDD). However, the risk for OSA in patients with chronic treatment resistant depression (cTRD) is not well documented worldwide.
Objectives: We assessed the risk for OSA and associated factors in cTRD patients.
Methods: The study recruited 140 Iranian patients with cTRD. All patients completed the Berlin questionnaire, which evaluates the risk of OSA. Additionally, demographic data and history of cardiovascular and metabolic diseases were collected. Pearson's Chi-square test, Fisher's exact test, and independent T-test were used to assess group differences, when appropriate.
Results: The study found that 89 of 140 cTRD patients (64%) were at high risk for OSA. Group comparison between cTRD patients (high vs. low risk for OSA) demonstrated that at high risk OSA-cTRD patients had an elevated rate of hypertension, diabetes mellitus, and obesity. Also, age, duration of depression, and duration of treatment were significantly higher in cTRD patients with higher risk compared to those with lower risk OSA" for "Also, age, duration of depression, and duration of treatment were significantly elevated in high versus low risk cTRD patients.
Conclusions: The results suggest that a noticeable number of patients with cTRD are at high risk for OSA, which is larger than the reported magnitude in the general population. Moreover, hypertension, diabetes mellitus, and obesity are associated with a higher risk for OSA. Also, age, treatment duration, and depression duration could be considered as possible comorbid factors for OSA in patients with cTRD.

Keywords: Berlin Questionnaire, Obstructive Sleep Apnea, Treatment-Resistant Depression

1. Background

Obstructive sleep apnea (OSA) is a chronic disorder caused by recurrent partial or complete pharyngeal obstruction during sleep (1). Obstructive sleep apnea is characterized by nocturnal apneas and hypopneas, intermittent hypoxia, reoxygenation and hyper-/hypocapnia events, as well as sleep fragmentation, which could lead to cerebral blood flow change, oxidative stress, systemic inflammation, vascular endothelial dysfunction, and increase in sympathetic nervous system activity (2-4). The prevalence of OSA in the general population is noticeable, which is 3% to 7% in males and 2% to 5% in females (5). Obstructive sleep apnea is considered as an independent risk factor for cardiovascular or metabolic comorbidities (6, 7). Moreover, OSA is an important risk factor for neurocognitive impairment and emotional decline (8, 9). Additionally, an elevated prevalence of OSA has been demonstrated in patients with various neurodegenerative diseases, such as Alzheimer's disease and neuropsychiatric disorders, including major depressive disorder (MDD), bipolar depression (BD), anxiety, posttraumatic stress disorder, and schizophrenia (10-15). The progressive change in sleep pattern due to OSA leads to alterations in cerebral blood flow, neurotransmitters profile, cellular redox status, and neural regulation. These changes are suggested to be contributing factors for development of neuropsychiatric disorders (3, 12).

Of all psychiatric disorders, evidence for increased rate of OSA is particularly strong for MDD (9, 12, 16). A recent meta-analysis including 12 studies with a total sample of 570,121, illustrated that the prevalence of OSA in serious mental disorders, including MDD, BD, and schizophrenia

was 25.7% and the aggregate prevalence was higher in MDD (36.3%) compared to BD (24.5%) or schizophrenia (15.4%) (11). Furthermore, MDD and OSA share a list of common symptoms, such as excessive daytime sleepiness, fatigue, loss of energy, cognitive dysfunction, irritability, insomnia, feelings of hopelessness, helplessness, sadness and decreased quality of life (17, 18). The common symptoms of OSA, such as daytime sleepiness and fatigue, are not always completely reversible with treatment (19). Moreover, many of such symptoms in MDD persist despite multiple treatment attempts (18, 20). Indeed, nearly one-third of individuals with MDD do not respond adequately to routine treatments (21, 22). Hence, comorbid depressive symptoms are frequently reported in patients with chronic medical disorders and sleep disorders, such as OSA (21, 23).

Treatment-resistant depression (TRD) is a term often used in clinical psychiatry to describe the refractory form of MDD (22). As mentioned, several studies have already investigated the association between MDD and coexisting OSA (18, 24-27). However, a few studies have examined if coexisting OSA could lead to treatment-resistance in MDD or a bidirectional association could be anticipated (i.e. patients with TRD are at high risk for OSA and OSA, which could lead to chronicity and treatment-resistance in depression) (28, 29). Although, the etiology of treatment resistance in depression has been studied in the context of inflammatory diseases, other possible causes of treatment resistance, including comorbidity with OSA has not been sufficiently studied worldwide (23, 30). Thus, this study examined the risk of OSA in Iranian patients with chronic TRD (cTRD) with a mean duration of depression of 8 years. Subsequently, the study compared medical comorbidities of OSA, including hypertension, diabetes mellitus, obesity, and cerebrovascular accident (CVA) in cTRD patients at high or low risk for OSA. Furthermore, the study assessed if patients with cTRD at high or low risk for OSA are different in gender, age, duration of depression, and treatment. To the best of our knowledge, risk of OSA has not been assessed particularly in patients with chronic TRD in Iran.

2. Objectives

The purpose of present study was to evaluate the risk for OSA and associated factors in cTRD patients.

3. Materials and Methods

3.1. Participants

Participants were 140 adult patients with cTRD (79 females and 61 males), which were recruited from the outpatient psychiatric clinic and psychiatric ward of the Farabi hospital, Kermanshah, Iran, between April, 2013 and August, 2014. All patients were diagnosed by a psychiatric interview using the structured clinical interview for diagnostic and statistical manual of mental disorders, 4th Edition, text revision (DSM-IV-TR). Inclusion criteria for chronic depression were either a major depressive episode lasting more than 12 months or dysthymia lasting more than 24 months (31). Moreover, patients were considered as treatment resistant when at least two antidepressants from different pharmacological categories had been administered for them, and less than 20% of their depressive symptoms after 4 to 6 weeks of treatment had been resolved (32). Patients with respiratory diseases, other psychiatric comorbidities, or substance use disorders were excluded.

The researchers collected demographic data, including age, gender, body mass index (BMI), duration of depression and treatment, as well as, history of cardiovascular, metabolic diseases, hypertension, diabetes mellitus, and CVA. All participants signed a written informed consent before beginning of the study. The research council and ethics committee of Kermanshah University of Medical Sciences (KUMS) approved this study.

3.2. Questionnaire

All participants completed the Berlin questionnaire for evaluating the risk for sleep apnea. The berlin questionnaire (BQ) is a widely used screening tool that assesses the risk of OSA in the general population (33, 34) and consists of 3 sleep and medical impairment categories. The BQ allows dividing patients to high and low risk for apnea based on their responses to different items and their overall scores in the symptom categories. The first category addresses snoring and observable apnea reported by a witness (5 items). The second category investigates daytime fatigue and sleepiness during daytime activities (3 items), and the third one assesses medical history (2 items: hypertension and BMI) as well as non-diagnostic information, such as age, gender, height, weight, and neck size. Each category is scored as either positive (present symptoms) or negative (absent symptoms). The first 2 categories are assumed positive, if the total score is more or equal to 2 in each category. The third category is considered positive for individuals with hypertension of $>$ 140/90 mmHg or BMI of $>$ 30 kg/m^2. Patients are classified as "high risk" for OSA if their scores are positive in at least 2 categories (34).

The English version of the BQ has been shown to have high sensitivity (86%), specificity (77%), positive predictive value (89%), and likelihood ratio (3.79) for screening OSA in the general population (34). The sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio of the Persian version of BQ were reported as 84.0%, 61.5%, 96.0%, 25.8%, 2.18%, and 0.26%, respec-

tively (35). A study has compared different screening questionnaires for OSA and found that the BQ has the highest specificity in predicting the risk for OSA compared to other psychometric variables (36).

3.3. Statistical Analyses

The data were analyzed using the SPSS version 20 software. Pearson's Chi-square test was used to evaluate the risk for OSA in patients with cTRD. Furthermore, Pearson's Chi-square test, Fisher's exact test, and independent T-test were used to compare cardiovascular and metabolic comorbidities and various risk factors of OSA in patients with cTRD, who showed high or low risk for OSA, when appropriate. At all levels of analyses, the alpha level was set to 0.05.

4. Results

Participants were adult patients with cTRD with an average age of 42.28 (SD = 9.22; range 24 to 66 years), including 79 females (mean age of 45.48; SD = 8.12), and 61 males (mean age of 38.13; SD = 8.95). Table 1 illustrates frequency of medical comorbidities of OSA, including hypertension, diabetes mellitus, obesity, and CVA, and Table 2 presents the descriptive information on gender, age, duration of depression, and treatment in male and female patients. There was a significant difference between genders based on duration of depression ($t(138) = 3.67$, $P < 0.01$, Cohens' $d = 0.59$) and duration of treatment ($t(138) = 2.47$, $P < 0.05$, Cohens' $d = 0.41$).

The sample by using the BQ indicated that 89 (64%) patients with cTRD were at high risk and 51 (36%) patients were at low risk for OSA, resulting in a significant difference between the groups ($X^2_{(1)} = 10.31$, $P < 0.01$). The high-risk group consisted of 52 females and 37 males, and the low-risk group included 27 females and 24 males.

In addition, Fisher's exact test compared the frequency of cardiovascular and metabolic diseases in patients with high and low risk for OSA. A significant difference in frequency was observed for history of hypertension ($X^2_{(1)} = 15.77$, $P < 0.01$(FET), $\varphi = -0.33$), diabetes mellitus ($X^2_{(1)} = 8.91$, $P < 0.003$ (FET), $\varphi = -0.25$) and obesity ($X^2_{(1)} = 32.32$, $P < 0.001$ (FET), $\varphi = -0.48$), yet not for CVA ($X^2_{(1)} = 1.75$, $P = 0.28$ (FET), $\varphi = -0.11$) or cardiovascular diseases ($X^2_{(1)} = 3.21$, $P = 0.128$ (FET), $\varphi = -0.15$). Moreover, the Pearson's Chi-square test showed no significant difference between high and low risk OSA groups ($X^2_{(1)} = 0.57$, $P = 0.39$, $\varphi = -0.05$). Taken together, patients with high risk for OSA were more likely to have a history of hypertension, diabetes mellitus, and obesity compared to patients with low risk for OSA. The φ coefficient indicated obesity had the strongest interaction with high risk for OSA. Details of results are illustrated in Table 3.

Table 1. Frequency of Participant's Medical Characteristics

Variables	Gender	Frequency	Percentage
Obesity			
No	Female	48	60.8
Yes, BMI > 30 kg/m^2		31	39.2
No	Male	48	78.7
Yes, BMI > 30 kg/m^2		13	21.3
No	Total	96	68.5
Yes, BMI > 30 kg/m^2		44	31.42
Hypertension			
No	Female	65	82.3
Yes		14	17.7
No	Male	52	85.2
Yes		9	14.8
No	Total	117	83.57
Yes		23	16.43
Cerebrovascular accident			
No	Female	76	96.2
Yes		3	3.8
No	Male	61	100
Yes		-	-
No	Total	137	97.85
Yes		3	2.15
Cardiovascular disease			
No	Female	62	78.5
Yes		17	21.5
No	Male	57	93.5
Yes		4	6.6
No	Total	119	85
Yes		21	15
Diabetes mellitus			
No	Female	73	92.4
Yes		6	7.6
No	Male	53	86.9
Yes		8	13.1
No	Total	126	90
Yes		14	10

Independent t-test comparing age, duration of treatment, and duration of depression among patients with high or low risk for OSA revealed a significant difference in age ($t(138) = 3.64$, $P < 0.001$, Cohens' $d = 0.61$), duration of treatment ($t(138) = 2.63$, $P < 0.01$, Cohens' $d = 0.45$), and

Table 2. Descriptive Information of Age, Duration of Treatment and Depression in Male and Female

Gender	Age, y	Duration of Depression, Y	Duration of Treatment, Mo
Female (n = 79)			
Mean	45.48	9.07	60.97
SD	8.12	5.50	49.03
Min	26	1.0	8.0
Max	62	20.0	180
Male (n = 61)			
Mean	38.13	7.12	43.13
SD	8.95	3.26	34.88
Min	24	1.0	3.0
Max	60	17.0	144
Comparison between genders			
T	5.07	3.67	2.47
P value	0.001	0.001	0.014
Cohens' d	0.86	0.59	0.41

Abbreviation: SD, Standard Deviation.

Table 3. Statistical Analysis Comparing the Frequency of Cardiovascular and Metabolic Diseases in Patients with High Versus Low Risk for Obstructive Sleep Apnea

Risk Factors	Risk for OSA		X^2	P Value	φ
	High	Low			
Hypertension			15.77	0.001	-0.33
Yes	23	0			
No	66	51			
Obesity			32.32	0.001	0.48
Yes	43	1			
No	46	50			
Diabetes mellitus			8.91	0.003	0.25
Yes	14	0			
No	75	51			
Cardiovascular disease			3.21	0.128	-0.15
Yes	17	4			
No	72	47			
Cerebrovascular accident			1.75	0.28	-0.11
Yes	3	0			
No	86	51			
Gender			0.57	0.39	0.05
Female	52	37			
Male	27	24			

duration of depression ($t(138) = 2.52, P < 0.05$, Cohens' d = 0.49). The mean age and duration of treatment and depres-

sion for patients with high risk for OSA was higher than low risk for OSA patients (Table 4).

5. Discussion

This study assessed the risk of OSA in patients with cTRD and the findings indicated that 64% were at a high risk for OSA. A positive link was demonstrated between high risk for OSA and the frequency of medical comorbidity, such as hypertension, diabetes mellitus, and obesity in patients with cTRD. Moreover, with older age or higher duration of depression and treatment, there is a higher risk for OSA. One should note that the sample were acquired from a hospital in Kermanshah, which is in the west of Iran. It has previously been demonstrated that the prevalence of symptoms and risk for OSA in the general population of Kermanshah is rather high (27.3%) (33, 37, 38). Based on the results, the risk for OSA in patients with cTRD is much greater than the general population of Kermanshah.

The main finding is consistent with studies reporting an increased incidence of OSA symptoms in patients with depression, building a long-standing co-occurrence of mood and sleep disorders (11, 24). The results are also consistent with studies indicating that untreated OSA patients might show higher depressive symptoms (39-41). Several studies have shown that existence of treatment resistant symptoms in patients with OSA might be due to depression and not due to OSA per se (42-44).

Poor sleep quality, sleep fragmentation, and intermittent hypoxemia have been proposed to influence mood (17, 18, 42, 44). The positive effect of continues positive airway pressure (CPAP) and oxygen supplementation treatment on psychological symptoms in patients with OSA and comorbid depression indicate that hypoxia might play an important role in depressive symptoms treatment-resistance (39, 43, 45). However, these treatments are not effective for a subset of patients with TRD and comorbid OSA. For example, it has been revealed that CPAP does not reduce depressive symptoms in patients with OSA and persistent depressive symptoms are linked with excessive daytime sleepiness. Habukawa et al. assessed the effect of CPAP treatment on patients with MDD and coexisting OSA and found that patients could be divided to responders and non-responders to CPAP. Moreover, they found that patients with MDD with a positive response to CPAP showed a more decreased percentage of Rapid Eye Movement (REM) sleep than non-responders (29). Rapid eye movement sleep plays an important role in modulating noradrenergic brain stem activity, and the activity of amygdala and medial prefrontal cortex, two regions crucial for detecting emotional salience. This is related to the findings of a meta-analysis on structural and functional abnormalities in OSA, which highlighted the role of the right amygdala, hippocampus, and insula in abnormal emotional and sensory processing in OSA (46). Recently, resting-state fMRI studies have been suggested that disrupted functional connectivity of the posterior default mode network is associated with cognitive and depressive symptoms of OSA (47). It has been discussed that OSA decreases the percentage of REM sleep, which results in dysfunction of brain circuitry related to emotion and mood regulation. Indeed, a few inhibitory and excitatory neurotransmitters, such as serotonin, norepinephrine, and γ-aminobutyric acid (GABA), alter the function of key regions involved in both sleep/wake cycle and mood regulation (48). Therefore, the imbalance of neurotransmitters might lead to co-occurrence of MDD and OSA. These findings indicate that although, all the TRD residual symptoms are not caused by OSA, patients with TRD could be at high risk for OSA and they should be evaluated for sleep apnea, particularly in subjects with loud snoring, medical diseases, fatigue, and daytime sleepiness.

Additional findings demonstrated a positive link between high risk for OSA and the frequency of medical comorbidity, such as hypertension, diabetes mellitus, and obesity. This is supported by evidence regarding the comorbidity of these medical conditions with both MDD and OSA (6, 49-54). This study observed that obesity is the strongest risk factor for OSA, as 43 of 44 obese patients with TRD were at high risk for OSA (Table 3). This result is convergent with previous studies presenting residual depression symptoms in patients with the higher BMI that are more likely to be affected by OSA than MDD (29, 54). Moreover, mean age, duration of treatment and depression were greater in patients with high risk for OSA (Table 4). Hence, the chronicity of depression and older age are related to higher risk for developing OSA. Similarly, it has been observed that depressed older patients with a prior diagnosis of OSA show a lower rate of response to antidepressant treatment compared to depressed patients without a diagnosis of sleep apnea, suggesting that OSA impairs response to antidepressants in depressed older adults (28). This is also consistent with another study, showing that OSA might be negatively associated with response to treatment with serotonin selective reuptake inhibitors in a mixed age population (55).

5.1. Study Limitations

One of the limitations was using the BQ to measure the risk for OSA in patients with cTRD. The BQ is a widely used screening tool to assess the risk for OSA in the general population (33, 34); although, its efficacy in patients with different psychiatric disorders has not been fully established.

Table 4. Descriptive Information of Age, Duration of Treatment and Depression in Patients with High and Low Risk for Obstructive Sleep Apnea

Risk for OSA	Age	Duration of Depression, Y	Duration of Treatment, Mo
High risk (n = 83)			
Mean	43.64	8.69	60.49
SD	7.77	4.84	42.45
Min	26	1	6
Max	62	20.0	144
Low risk (n = 51)			
Mean	38.69	7.35	40.41
SD	10.13	4.38	43.83
Min	24	1.0	3.0
Max	60	18.0	180
Comparison between genders			
T	3.64	2.63	2.52
P value	0.001	0.01	0.05
Cohens' d	0. 61	0.45	0.49

Abbreviation: SD, Standard Deviation.

Best et al. have evaluated the efficacy of the BQ in predicting OSA among 82 outpatients with TRD (30), and found that the BQ is able to predict OSA with specificity greater than 85% and sensitivity of 24%. Therefore, BQ can be considered highly specific, which is an important factor for validity of the screening tool. However, the sensitivity of the BQ is not high and may lead to false positive results. Despite this low sensitivity, the current findings are valid given that BQ was used as a screening tool for the risk of OSA not OSA itself. However, the self-rating measure is not a gold standard for OSA diagnostic purpose (56). Thus, future studies should test the OSA-cTRD link using objective tools, such as polysomnography to ascertain for OSA.

Another limitation was that this study did not control for different types of therapeutic regimens that may have altered the risk for OSA (e.g., first or second generation antidepressant, dosage of antidepressants, usage of additional antipsychotics, or alternative approaches, such as electroconvulsive therapy or repeated transracial magnetic stimulation). Smoking (current use or history of), an obvious risk factor for OSA, was another confounder in the current study that was not controlled; in fact, there were high rates of smoking in the patients with cTRD. Moreover, this study included both MDD and dysthymic patients and did not control for their difference. Given the nature of their treatment and symptom history, future studies should differentiate these 2 groups based on OSA symptom severity.

5.2. Conclusion

The current study demonstrated that 64% of patients with cTRD were at high risk for OSA, which is larger than the risk for OSA in the general population. Besides, hypertension, diabetes mellitus, and obesity were associated with higher risk for OSA in cTRD patients. This study recommends screening and early diagnosis of OSA in patients with TRD to avoid its adverse effects on health and quality of life, as well as better management of depression.

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Footnotes

Authors' Contribution: Habibolah Khazaie and Masoud Tahmasian conceived and designed the study. Hossein Alavi-Mehr and Golrokh Younesi collected the data. Akram Soleimani, Hadi Mozafari, and Fateme Samea performed the statistical analysis. Habibolah Khazaie, Amir Ali Sepehry, Fateme Samea, and Masoud Tahmasian drafted the manuscript and revised it. All authors read and approved the final manuscript.

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