

The effects of depression, anxiety and sleep disturbances on cognitive impairment in patients with chronic obstructive pulmonary disease

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Abstract The purpose of this study was to investigate the effects of depression, anxiety and sleep disturbances on cognitive functions in chronic obstructive pulmonary disease (COPD) patients. In this prospective case-control study, demographic data, smoking history, depression, anxiety, sleep quality and cognitive status of 48 COPD patients and 36 healthy volunteers aged 40–90 years were recorded. The Beck depression inventory (BDI), the Beck anxiety inventory (BAI), and Pittsburgh Sleep Quality Index (PSQI) were used to assess depression, anxiety and sleep quality, respectively in COPD patients. Cognitive performance was studied by the mini-mental state examination. The mean age of patients with COPD was 65.3 ± 9.4 years, and disease duration was 9.6 ± 7.8 years. Male sex ratio, smoking, BDI score, BAI

score, total PSQI score, sleep latency, sleep duration, average use of sleep aids and sleep disturbances in patients with COPD were significantly higher than the control group ($p < 0.05$). When cognitive impairment was compared by age, FVC, FEV, FEV/FVC, PEF values and smoking, no statistically significant relationship was found ($p > 0.05$). A statistically significant relationship was established between cognitive impairment and severity of disease, presence of anxiety, presence of depression and sleep quality. In our study, we found that sleep disorders, depression and anxiety comorbid with COPD increased cognitive impairment as well as the severity of disease. We believe that this finding is important in terms of reducing the risk of cognitive impairment, preventing misdiagnosis and treatment of the aforementioned comorbid diseases.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a multicomponent disease, and patients may present with a variety of comorbid conditions that can affect prognosis and increase the risk of mortality (Divo et al. 2012). Cognitive impairment is noted as an increasingly prevalent comorbidity in COPD (Dulohery et al. 2015). The prevalence of cognitive impairment in patients with COPD ranges from 12 to 88%. This variability in prevalence is associated with depression and poor quality of life, which may affect patients' ability to manage the disease, reduced compliance with medication and oxygen therapy, which may worsen clinical course (Roncero et al. 2016). Psychological dysfunction is likely to be seen as both a

complication of COPD and a symptom of a chronic disease. Comorbid psychological disorders have been associated with increased functional impairment, disability, morbidity, poor quality of life and reduced compliance with treatment in patients with COPD (Smith et al. 2014; Panagiotti et al. 2014; Tselebis et al. 2016).

Sleep disorders are common in patients with COPD, and these patients have been reported to have more difficulty in falling, maintaining and staying asleep and also experience more daytime sleepiness (Price et al. 2013). Possible reasons of high prevalence of sleep disorders are advanced age of patients, pharmacotherapy, COPD-specific symptoms such as wheezing and coughing, COPD-related comorbid conditions such as sleep apnea and psychiatric symptoms associated with hypoxemia. Poor quality of sleep was correlated with poor quality of life in COPD patients (Nunes et al. 2009).

Sleep disorders, depression and anxiety can individually lead to deterioration in cognitive functions. Sleep and sleep-wake rhythm disturbances increase the risk of dementia and cognitive decline in the elderly population. Similarly, both depression and anxiety are associated with higher rates of cognitive impairment process leading to Alzheimer's disease (Guarnieri and Sorbi 2015; Orgeta et al. 2015). When we searched comorbid diseases increasing cognitive impairment in COPD patients, we didn't find any study which assessed depression, anxiety and sleep disorder together in the literature.

The aim of this study was to investigate the effects of depression, anxiety and sleep disturbances on cognitive impairment in COPD patients.

Materials and methods

This study was conducted at the respiratory and neurology outpatient clinics of Sakarya Training and Research Hospital between January 2015 and January 2016. 48 patients aged 40–90 years, who were followed up for at least 1 year upon diagnosis of COPD, and 36 healthy controls were included in this prospective case-control study.

The study was approved by Sakarya University Human Ethics Committee. A detailed written informed consent was obtained before the respective subject's participation in the study. The study was conducted in accordance with the principles of the declaration of Helsinki.

Inclusion criteria were: age >40, diagnosis of COPD as defined in the global initiative for chronic obstructive lung disease (GOLD) guidelines (Vestbo et al. 2011), ability to complete Mini-Mental test, oxygen saturation >90%, no obstructive sleep apnea, no chronic disease comorbid with COPD. Exclusion criteria were inability to provide informed consent, inability to complete cognitive tests

because of speech or vision problems, any neurological and psychiatric disorders, the use of medicines that could affect cognitive tests (lithium, antihistamines, sedatives, etc.), alcohol and substance abuse and inability to complete pulmonary function tests. Demographic data, body mass index (BMI), smoking history of the patient group and the control group were recorded.

Pulmonary function tests

Pulmonary function tests were performed by Spirolab III spirometry (Spirolab; Medical International Research, Rome, Italy) according to the criteria of American Thoracic Society/European Respiratory Society (Miller et al. 2005). Forced vital capacity (FVC), FEV₁, FEV₁/FVC rate, peak expiratory flow (PEF), and forced expiratory flow between 25 and 75% of FVC (FEF 25–75%) were recorded. Severity of COPD was determined on the basis of GOLD burden criteria. Patients were grouped into four categories: A: Low risk, low symptom burden; B: Low risk, higher symptom burden; C: High risk, low symptom burden; D: High risk, higher symptom burden.

Assessment of depression- anxiety

Depression symptoms and anxiety symptoms were evaluated using the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI), respectively. Beck depression and anxiety inventories consist of 21 questions and are scored between 0 and 63 points. Depression cut-off value was taken as BDI \geq 10 points, and anxiety disorder cut-off value was taken as BAI \geq 17 points (Beck et al. 1988; Beck and Steer 1984).

Assessment of Sleep disturbances

Sleep quality was evaluated by Pittsburgh Sleep Quality Index (PSQI). PSQI was scored between 0–21 points, and a score >5 points was evaluated as poor sleep quality. Index consists of 7 headings, including sleep quality, sleep duration, sleep latency, self-estimated sleep efficiency, use of sleep aids, daytime dysfunction and sleep disturbances (Buysse et al. 1989).

Assessment of cognitive assessment

Mini-Mental Status Examination (MMSE) was applied to COPD patients for the evaluation of cognitive functions. MMSE is the best-known, commonly used short-duration rating scale which assesses cognitive impairment in clinical assessment and research. This scale consists of 12 chapters and 30 questions in which spatial and temporal orientation, attention, registration, calculation, repetition,

language and visual construction are assessed. The test is evaluated over 30 points, with each correct answer rated with 1 point (Nieuwenhuis-Mark 2010).

In our study, the cut-off value for cognitive impairment in patients with COPD was considered to be 24 and below. The group with a MMSE score of ≤ 24 was compared by FVC, FEV, FEV/FVC, PEF values, all subtypes of PSQI, BDI and BAI scores.

Statistical analyses

Statistical analyses were carried out using the SPSS/PC software (version 21.0). Descriptive statistics were presented as mean values with a standard deviation for numeric variables. Independent *t* tests were used to examine the difference between the categorical variables having two groups; whereas, one-way ANOVA test (one-way analysis of variance) was used for examining the difference between the categorical variables having more than two groups. While Chi square test was used for examining the correlation between the two categorical variables, Pearson Correlation Coefficients were used for examining the correlation between the two numerical variables. The limit for statistical significance was accepted as $p < 0.05$. In order to investigate the effect of the independent variables on this dependent variable, the multiple regression analysis was used.

Results

General characteristics, cognitive status, depression, anxiety and sleep quality scores of the patient group and the control group are shown in Table 1. The mean age of patients with COPD was 65.3 ± 9.4 years, and disease

Table 1 General characteristics, cognition, depression, anxiety and sleep quality of patients with COPD and healthy controls

	COPD (n:48)	Controls (n:36)	<i>p</i> value*
Gender (M/F)	(38/10)	(19/17)	0.044
Age	65.3 ± 9.4	66.2 ± 11.4	0.518
Onset age	40.91 ± 13.6	–	
Duration of disease	7.35 ± 7.51	–	
PSQI total score	6.04 ± 5.17	2.52 ± 2	0.001
MMSE score	25.3 ± 3.2	27.9 ± 1.8	0.001
BAI score	13.45 ± 7.28	7.97 ± 5.74	0.001
BDI score	11.64 ± 7.28	7.97 ± 5.74	0.001

COPD chronic obstructive pulmonary disease, PSQI Pittsburgh sleep quality index, MMSE mini mental status test, BDI Beck's depression inventory, BAI Beck's anxiety inventory

* $p < 0.05$, statistical significance, with Student's *t* test

duration was 9.6 ± 7.8 years. Male sex ratio, smoking, BDI score, BAI score, total PSQI score, sleep latency, sleep duration, average use of sleep aids due to sleep disorders in patients with COPD were significantly higher than the control group ($p < 0.05$) (Table 1).

The comparison of all PSQI subtypes of patients with COPD and healthy controls are shown in Table 2.

Mean cognitive function score, as measured by the MMSE, was 25 ± 3.2 , and 16 patients (33.3%) were found to have a score below the cut-off value specified as 24 points.

COPD patients were classified by the severity of disease according to GOLD criteria as follows: 6 patients (12.5%) in Group A; 7 patients (14.6%) in Group B; 20 patients (41.6%) in Group C and 15 patients (31.3%) in Group D. When the severity of disease and cognitive dysfunction were compared, a statistically significant positive and moderate relationship was found between them ($p < 0.05$, $r = 0.302$).

When cognitive impairment (MMSE < 24) was compared with age, FVC, FEV, FEV/FVC, PEF values and smoking, no statistically significant relationship was found ($p > 0.05$).

Cognitive impairment and depression- anxiety

A statistically significant positive and moderate relationship was established between anxiety and cognitive impairment (BAI > 17) ($p < 0.05$, $r = 0.340$).

When cognitive impairment was compared with the presence of depression (BDI > 10), a statistically significant relationship was found ($p < 0.05$, $r = 0.418$) (Table 3).

Cognitive impairment and sleep disturbances

Statistically significant positive and moderate level of relationships were established between cognitive impairment and total sleep quality, sleep duration and sleep latency ($p < 0.05$, $r = 0.418$, $r = 0.440$, $r = 0.351$). Similarly, when cognitive impairment was compared with the group with PSQI > 5 points, statistically significant relationships were found between them ($p < 0.05$, $r = 0.505$).

Statistically positive relationships were identified between cognitive impairment and sleep disturbance, subjective sleep quality, self-estimated sleep efficiency and daytime dysfunction ($p < 0.05$, $r = 0.263$, $r = 0.428$, $r = 0.334$, $r = 0.334$).

No statistically significant relationship was found between cognitive impairment and the use of sleep aids ($p > 0.05$) (Table 4).

When total effect of the variables, which were found to be effective on cognitive impairment according to

Table 2 Sleep quality of patients with COPD and healthy controls

	COPD group n = 48	Control group n = 36	<i>p</i> value
PSQI total score	6.04 ± 5.2	2.52 ± 2.6	0.001
PSQI sleep latency	1.10 ± 1.2	0.63 ± 0.9	0.041
PSQI sleep duration	0.77 ± 0.9	0.30 ± 0.6	0.008
PSQI sleep disturbances	1.43 ± 1.1	0.44 ± 0.6	0.001
PSQI use of sleep aids	0.16 ± 0.6	0.08 ± 0.3	0.440
PSQI self-estimated sleep efficiency	1.52 ± 0.5	1.83 ± 0.4	0.002
PSQI sleep quality	1.02 ± 1.0	0.69 ± 0.8	0.109
PSQI daytime dysfunction	0.54 ± 0.8	0.00 ± 0	<0.001

COPD chronic obstructive pulmonary disease, *PSQI* Pittsburgh sleep quality index

Table 3 Evaluation of factors affecting cognitive changes in COPD patients and control group

	BDI	BAI	PSQI score	Age	Smoking	Disease severity	FVC	FEV ₁
MMSE score								
COPD								
<i>r</i>	0.418	0.340	0.418	0.132	0.116	0.302	0.352	0.144
<i>p</i>	0.001	0.002	0.003	0.4	0.561	0.005	0.056	0.330
Control								
<i>r</i>	0.312	0.121	0.390	0.104				
<i>p</i>	0.005	0.4	0.007	0.546				
Cognitive impairment (MMSE < 24)								
COPD								
<i>r</i>	0.421	0.271	0.365	0.350	0.112	0.409	0.018	0.212
<i>p</i>	0.001	0.052	0.001	0.015	0.452	0.004	0.902	0.148
Control								
<i>r</i>	0.290	0.144	0.350	0.124				
<i>p</i>	0.038	0.330	0.016	0.602				

COPD chronic obstructive pulmonary disease, *PSQI* Pittsburgh sleep quality index, *MMSE* mini mental status test; *BDI* Beck's depression inventory, *BAI* Beck's anxiety inventory, *FVC* forced expiratory capacity, *FEV₁* forced expiratory volume in 1 s

regression analysis, was compared with cognitive impairment, the relationship between them was found to be markedly significant ($R = 0.643$, $R^2 = 0.403$, $F_{(11-72)} = 4.410$, $p < 0.01$). The effect of these variables on cognitive impairment was 40%. Only an independent relationship between severity of disease and presence of sleep disturbance and cognitive deterioration was detected (Table 5).

Discussion

In this study, the effects of COPD severity, sleep disturbance, depression and anxiety on cognitive impairment were investigated. A statistically significant relationship was found between cognitive decline ($MMSE < 24$) and the severity of COPD, depression, anxiety, total sleep quality, sleep duration and sleep latency, sleep disturbance,

subjective sleep quality, self-estimated sleep efficiency and daytime dysfunction. The total effect of all factors analyzed according to regression analysis on cognitive impairment was found to be statistically significant.

The relationship between cognitive dysfunction and COPD can be explained by several possible mechanisms. An important mechanism proposed for the cognitive impairment in patients with COPD is the neuronal damage caused by chronic hypoxemia associated with respiratory failure. In addition, recent studies have shown that COPD is associated with reduced hippocampal and gray matter volumes, and this was found to correlate with cognitive dysfunction. Furthermore, there are also hypotheses indicating that smoking, diabetes and cardiovascular diseases associated with chronic respiratory diseases may cause cognitive impairment (Yin et al. 2016). In our study, no correlation was found between cognitive impairment and smoking and respiratory function test values. The

Table 4 The effects of all PSQI subtypes on cognition in COPD patients

	Cognitive impairment (MMSE < 24)	MMSE score
PSQI total score		
<i>r</i>	0.418	0.365
<i>p</i>	0.003	0.01
PSQI total score		
<i>r</i>	0.505	0.409
<i>p</i>	<0.001	0.004
PSQI sleep duration		
<i>r</i>	0.289	0.430
<i>p</i>	0.008	0.002
PSQI sleep latency		
<i>r</i>	0.351	0.223
<i>p</i>	0.001	0.128
PSQ sleep disturbances		
<i>r</i>	0.440	0.750
<i>p</i>	<0.001	0.613
PSQI sleep quality		
<i>r</i>	0.428	0.348
<i>p</i>	<0.001	0.015
PSQI use of sleep aids		
<i>r</i>	0.153	0.403
<i>p</i>	0.165	0.005
PSQI self-estimated sleep efficiency		
<i>r</i>	0.334	0.358
<i>p</i>	0.002	0.013
PSQI daytime dysfunction		
<i>r</i>	0.289	0.244
<i>p</i>	0.008	0.009

COPD chronic obstructive pulmonary disease, PSQI Pittsburgh sleep quality index, MMSE mini mental status test

relationship between increased severity of COPD determined by GOLD staging and cognitive impairment was found to be statistically significant. Patients with no comorbid chronic disease and PaO₂ above 90% were included in this study and thus the effects of these parameters on cognition were excluded. In a well-conducted cross-sectional analysis, 36% of patients with moderate to severe COPD were found to have mild cognitive impairment (versus 12% in controls) (Villeneuve et al. 2012). A recent study demonstrated that both prevalence and severity of cognitive impairment in patients with various severity of COPD are directly associated with pulmonary condition, primarily hypoxemia. In the same study, it was established that many areas of cognition are affected and many functions are likely to deteriorate greatly (Dal Negro et al. 2014). Our study was consistent with previous studies and COPD was found to be an

Table 5 Regression analysis: evaluation of risk factors associated with cognitive deterioration in COPD patients

Variables	<i>p</i> value
PSQI total score	0.967
BAI	0.343
BDI	0.191
Severity of disease	0.008
Presence of sleep disturbance	0.019
PSQI sleep latency	0.468
PSQI sleep duration	0.317
PSQI sleep disturbances	0.647
PSQI sleep quality	0.746

Bold indicates statistical significant value

COPD chronic obstructive pulmonary disease, PSQI Pittsburgh sleep quality index, BDI Beck's depression inventory, BAI Beck's anxiety inventory

important risk factor that increases the risk of cognitive impairment.

Cognitive impairment is a critical healthcare burden in terms of costs. Cognitive impairment in COPD patients has been associated with poor prognosis, increased disability and mortality. Therefore, early diagnosis of this condition in patients with COPD is vital for prevention of morbidity and clinical course leading to dementia. Recognition of factors affecting cognition allows early detection of cognitive dysfunction and differentiation of high-risk COPD patients (Roncero et al. 2016). Several studies in the literature associated depression, anxiety disorder and sleep disturbance individually with cognitive impairment in COPD patients (Smith et al. 2014; Panagioti et al. 2014; Nunes et al. 2009; Guarnieri and Sorbi 2015). Our study is different from those studies in that our study is the first study that investigated the effects of these parameters together on the cognitive impairment and demonstrated that these factors increase the cognitive impairment both individually and as a whole.

In COPD patients, anxiety is closely linked with acute dyspnea attack, especially the sense of suffocation and the fear of death (Tselebis et al. 2016). Generalized anxiety disorder and panic disorder were found to be more common in patients with COPD than the general population (Panagioti et al. 2014).

Studies that compared depressive disorders with chronic diseases showed that COPD patients suffer from depression and mood symptoms at a higher rate (Tselebis et al. 2016). Although smoking, hypoxia and inflammation have a significant impact on the prevalence of depression in COPD patients, the strongest predictors of depression were shown to be symptom severity and quality of life in COPD (Hanania et al. 2011). Depression in patients with COPD leads to feelings of hopelessness and pessimism, decreased

appetite, reduced sleep, difficulties in concentration, increased lethargy, social withdrawal, decreased performance in daily activities and poorer health conditions (Tselebis et al. 2016). In our study, higher rates of depression and anxiety were obtained for the COPD patients, compared with the healthy control group.

Depression and anxiety are common in patients with dementia and mild cognitive impairment (MCI). Both depression and anxiety were associated with higher rates of progression to Alzheimer's disease in MCI patients (Orgeta et al. 2015).

Our study showed that depression and anxiety disorder were more common in patients with COPD and increased the risk of cognitive impairment. According to these results, which are consistent with previous studies, we think that early detection and treatment of depression and anxiety in patients with COPD are essential in order to reduce the risk of the cognitive impairment and burden of disease.

Sleep disorders are highly prevalent in COPD patients and they often have poor sleep quality. Sleep problems may reduce the quality of life. About 50% of COPD patients were found to have longer sleep latency, more frequent awakenings and daytime sleepiness (Urbano and Mohsenin 2006). Klink and Quan showed that 39% of COPD patients with nocturnal cough or wheezing had difficulty in initiating and maintaining sleep and 29% of the patients had daytime sleepiness (Klink and Quan 1987). In a case-control study where 52 patients with mild to moderate COPD were compared with 52 healthy controls, COPD patients were found to have reduced sleep efficiency, total sleep time and mean nighttime oxygen saturation. Also, COPD patients were reported to have more difficulty in initiating and maintaining sleep (Valipour et al. 2011).

In a cohort study which investigated sleep quality rated by PSQI in COPD patients, markedly reduced sleep quality, prolonged sleep latency, decreased sleep duration, a decline in total PSQI score, a lower rate of daytime sleep and dysfunction were determined (Geiger-Brown et al. 2015). In our study, a significant relationship was established between cognitive decline and total sleep quality, sleep duration and sleep latency, sleep disorder, subjective sleep quality, self-estimated sleep efficiency and daytime dysfunction, which we rated with PSQI. These findings are in good correlation with previous studies in the literature, which reported that sleep disorders are quite common in all types of dementia, mainly Alzheimer's disease (Guarnieri and Sorbi 2015). Despite their high-frequency, pathogenic role, clinical and social impact, sleep disorders can not be assessed systematically and carefully in clinical practice. Taken together, the results of our study suggest that any early and progressive abnormalities to be detected

in sleep circadian rhythm, quality, architecture and neural regulation are likely to be beneficial and prognostic indicators of cognitive impairment and dementia, which is in line with the literature (Guarnieri and Sorbi 2015).

The strengths of our study include the following: Rich data were studied in patients with various severity of COPD despite the low number of patients; sleep quality, emotional status and cognitive impairment were performed by the same physician in a detailed and systematic way; other comorbid conditions that may cause cognitive deterioration as well as conditions such as sleep apnea syndrome were ruled out.

Our study has several limitations. First, we worked with a relatively small sample and male gender was dominant among our cases. This reflects the normal frequency in clinics, as revealed by previous studies conducted in Turkey, which reported male gender as dominant among COPD patients (Deveci et al. 2011), however, further studies are needed to assess both genders in larger groups of patients. Another potential shortcoming was the fact that only MMSE was used to rate cognition. MMSE has been criticized as being an insufficient screening test for patients with cognitive impairment because of its low sensitivity especially in early stages of COPD (Ihara et al. 2013). Additional psychometric tools would be much more suitable and more robust.

Conclusion

Cognitive impairment, which is an important factor affecting the course of COPD, is associated with poor quality of life, hospitalization and lower survival rate. Early detection of cognitive decline can help improve daily life by individualization of treatment and care advice. In our study, we found that sleep disorders, depression and anxiety comorbid with COPD increased cognitive impairment by 40% along with the severity of disease. We think that this result is important in terms of reducing the risk of the cognitive impairment by early diagnosis and treatment of the aforementioned comorbid diseases, prevention of misdiagnoses and reducing the care burden likely to arise from dementia.

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