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Chronic Obstructive Pulmonary Disease and Sleep Quality

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<http://dx.doi.org/10.5772/57559>

1. Introduction

Sleep is a basic physiological need for all humans. People need to sleep and rest enough for a healthy and productive life. However, some factors may prevent attainment of adequate sleep and rest. While some of these factors may cause transient alterations in an individual's sleep-rest routine, other factors can affect sleep chronically. Chronic systemic diseases are one of the most important factors that can affect the characteristics of people's sleep for a long-time period. Chronic diseases cause various sleep problems and impair sleep quality. One of the chronic systemic diseases that affects the sleep routine and sleep quality of people severely is Chronic Obstructive Pulmonary Disease (COPD).

COPD is an important health problem with an increasing prevalence and high morbidity and mortality rate all over the world. In the last 20 years, the increasing mortality rates related to COPD emphasize that COPD is a growing health problem [1]. WHO predicts that COPD will become the third leading cause of death worldwide by 2030 [2]. The Global Initiative for Obstructive Lung Disease (GOLD) characterizes COPD as "a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. The pulmonary component of COPD is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases". [3]

COPD, which affects individuals multidimensionally, has severe consequences. The complaints of patients with COPD are not limited to the symptoms of dyspnea, cough and phlegm production [4]. Although COPD is a disease affecting primarily the respiratory tract and lungs, it has many systemic effects and complications related to the cardiovascular system, musculoskeletal system, neurological system, nutrition, and metabolism [5,6].

COPD severely affects the social and psychological aspects of patients' lives as well as their physical health. Due to the changes of the disease process, COPD forces patients to make changes in their lifestyles. Due to the stress, anxiety, loss of control and independence, change of sense of self, and respiratory distress, patients experience important psychological alterations including serious fear of death and depression [4,7-9]. Patients with COPD have to change most of their daily activities due to dyspnoea, functional impairment, and fatigue. With increasing fatigue and dyspnoea, they adopt a sedentary lifestyle [4]. Many patients with COPD have poor sleep quality, especially those who have high anxiety and depression [10-12]. Shackell et al (2007) stated that the anxiety experienced due to dyspnoea affects the sleep quality of patients with COPD and the sleep quality has effects on physical and emotional functions [13]. COPD-related sleep disturbances play a role in its morbidity and adversely affect quality of life. Poor sleep quality could contribute to poor COPD-related outcomes such as exacerbations or even mortality risk [14].

2. Oxygen desaturation during sleep in COPD patients and sleep problems

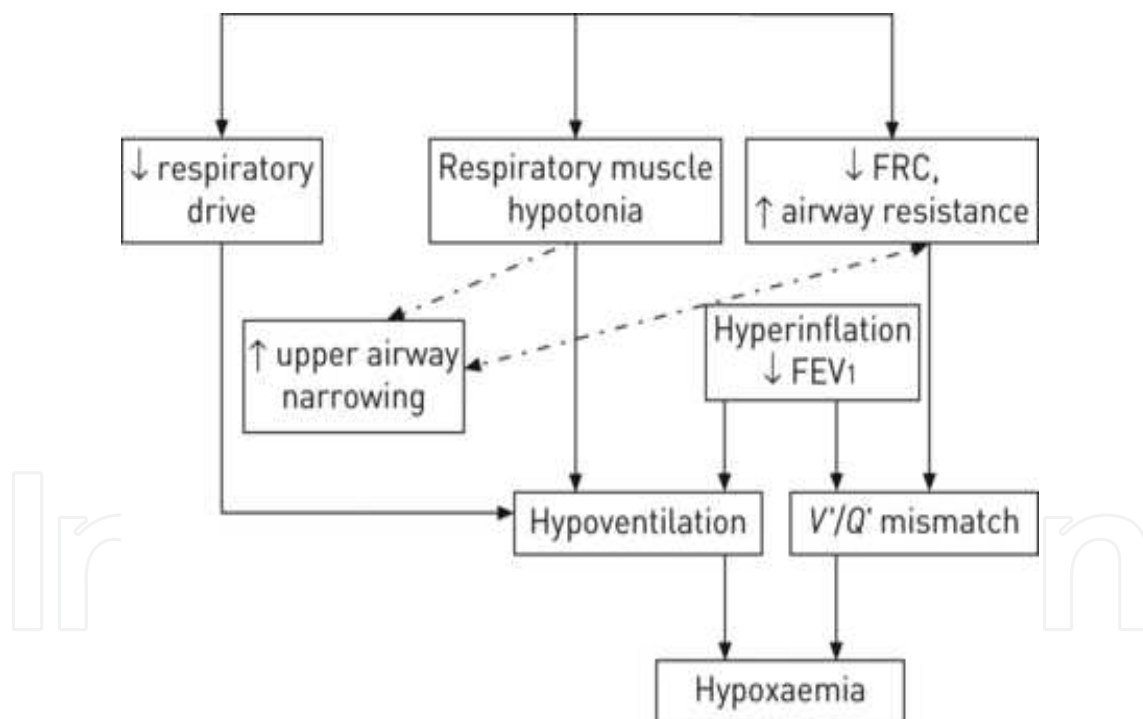
Sleep is a physiological situation that occurs depending on the special functional organization of the central nervous system. Each individual feels the need to sleep later in the evening and sleeping occurs generally at night [15]. Normal sleeping is divided into non-rapid eye movement (NREM) and rapid eye movement (REM). NREM consists of three stages: N1, N2 and N3 (quiet sleep or delta sleep). Strong stimuli are required to wake up someone whose NREM stages proceed. REM has tonic and phasic components. REM sleep has a parasympathetically mediated tonic component and sympathetically mediated phasic component. The phasic component of REM sleep is characterized by skeletal muscle twitches, increased heart rate variability, pupil dilation, and increased respiratory rate [16-18]. During NREM sleep, the metabolic demand of the brain decreases and the blood flow throughout the entire brain progressively decreases [19-21].

In order to understand the effect of COPD on respiration during sleep, one should principally know the physiological changes occurring during the periods of regular sleep and wakefulness. While the respiratory system provides the oxygen that the body needs on one part, it helps remove the carbon dioxide produced by the body's metabolic processes on the other part. Arrangement of the functions of the respiratory system basically occurs through negative feedback [3]. Ventilation is normally controlled by a combination of two systems: a metabolic system responsible for the automatic changes directly related to gas exchange, and a behavioral system responsible for the voluntary changes originating from cortical and forebrain structures [22-23].

While metabolic rate decreases during sleep, responses to various chemical, mechanical, and cortical stimuli also decrease. The respiratory response to the changes observed in the partial oxygen and partial carbon dioxide pressures in the arterial blood differs significantly in comparison to the wakefulness period [24]. Especially during REM sleep, such physiological changes may affect gas exchange and lead to hypoventilation resulting in clinically significant hypoxemia and hypercapnia in patients with COPD [25].

The most pronounced hypoxemia occurs during the REM stage of sleep because of the generalized muscle hypotonia that accompanies this stage [26]. REM-associated hypoxemia can reach critically low levels, especially in patients with already borderline waking oxygenation, with potentially deleterious clinical consequences such as cardiac dysrhythmias, pulmonary hypertension, and polycythemia [21,26].

Sleep affects respiration through changes in control of the respiratory center, in airway resistance, and in muscle contractility. These changes which usually are not consequential in healthy people may cause problems in patients with COPD. The gas exchange which occurs during sleep in patients with COPD arises as a result of the nature of the disease [3,27]. In COPD, breathing against expiratory airflow obstruction becomes more difficult during sleep when there is reduced tidal volume, ineffective ventilation, and hypoxemia [28]. Patients with COPD experience the most profound hypoxemia and hypercapnia during REM sleep [26]. The oxygen desaturation which occurs during sleep in COPD may be greater than that which occurs during maximal exercise [29]. This desaturation predisposes to cardiac arrhythmias at night [28,30], pulmonary hypertension [28,31,32] and probably deaths during acute attacks [33].



FRC=functional residual capacity; FEV₁=forced expiratory volume in 1 s; V'/Q'=ventilation/perfusion ratio;(McNicholas et al. Sleep disorders in COPD: the forgotten dimension. *European Respiratory Review*. 2013,22(129):365-375.)

Figure 1. Pathophysiology of sleep-related respiratory changes in chronic obstructive pulmonary disease.

COPD patients develop hypoxia and hypercapnia of varying degrees depending on the severity of their lung disease; hyperinflation occurs in the lungs due to air trapping and work of breathing increases [3]. Oxygen desaturation among the COPD patients is probably

caused by physiologic hypoventilation that occurs during sleep precipitating a considerable decrease in the SaO_2 level of hypoxemic patients [28,34,35]. Hypoventilation during sleep is related to impairment of the respiratory center's response to chemical, mechanical and cortical stimuli [26,36, 37].

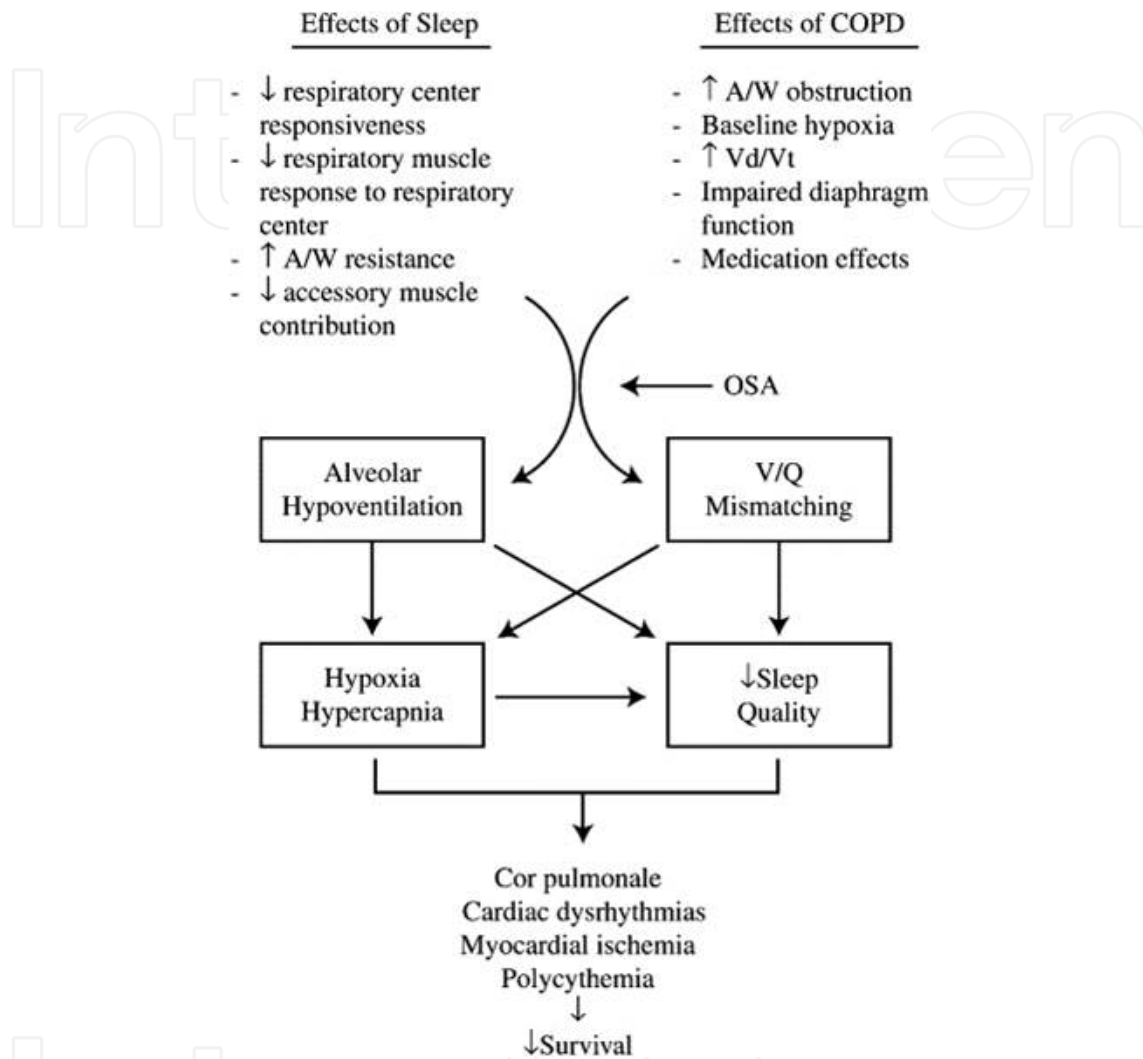
During sleep, ventilation/perfusion relationships are deranged. Especially in REM sleep, atony of accessory respiratory muscles develops decreasing functional residual capacity which further worsens ventilation/perfusion relationships, and hypoxemia intensifies. Decrease of intercostal muscle activity is important in patients with COPD who rely upon the use of accessory respiratory muscles to maintain respiration. Lung hyperinflation places the diaphragm, the only functioning respiratory muscle during REM sleep, at a mechanical disadvantage that also impairs oxygenation through alterations in ventilation/perfusion matching [26,37]. The compensatory efforts of the muscles that assist the diaphragm and hyperinflated lungs become inefficient after time [18,38]. The diaphragm is at a mechanical disadvantage due to lung hyperinflation which adversely affects the contractile power of diaphragmatic muscle fibres (type I fibres). Such changes are of paramount importance as they restrict the effectiveness of the diaphragm during respiration [39,40]. In order to maintain respiratory effort, patients utilize accessory muscles in the chest, shoulder and abdomen. Due to atony, accessory muscles of respiration are unable to augment respiration during REM sleep which results in flattening of the diaphragm. Because the diaphragm is unable to contribute to ventilation during REM sleep, minute ventilation declines to half the daytime level. In addition, this reduction in ventilation is accompanied by deranged ventilation/perfusion (V/Q mismatch) and adequate gas exchange does not occur. As a result, arterial oxygen decreases and carbon dioxide increases. These derangements in gas exchange are more prominent among patients with COPD compared with the general population [21,38].

Drugs such as corticosteroids, methyl xanthenes and β -agonists which are used in the treatment of COPD also affect the sleep of the patient [41,42]. They can disrupt sleep and provoke sleeplessness irrespective of the severity of the patient's respiratory disease [3].

In patients with COPD, nocturnal desaturation and moderate hypoxemia are associated with an increase in pulmonary artery pressures [31,43,44]. In COPD patients, this hypoxemia associated rise in pulmonary arterial pressures is reversed with oxygen treatment [37]. In addition, in patients with COPD, premature ventricular contractions increase during sleep and oxygen treatment reduces their frequency [30].

The presence of other health problems that accompany COPD affects the occurrence and severity of sleep disorders. Patients with sleep apnea who do not have COPD experience rapid normalization of oxygen levels after apnea associated desaturations. However, in patients who suffer from both COPD and sleep apnea, apnea associated oxygen desaturation is more profound and longer because these patients are already hypoxic when the apnea begins. Therefore, patients with COPD are at risk for complications caused by chronic hypoxia like cor pulmonale and polycythemia [37].

Krachman et al summarized the potential consequences of changes in ventilatory control and respiratory muscle function during sleep in patients with chronic obstructive pulmonary disease (COPD) in Figure 2. [21]



A/W=airways; OSA=obstructive sleep apnea. V/Q=ventilation/perfusion ratio. Vd/Vt=ratio of dead space volume to tidal volume.

(Krachman et al. Sleep abnormalities and treatment in emphysema. Proc Am Thorac Soc, 2008, 5(4):536-542)

Figure 2. Potential consequences of changes in ventilatory control and respiratory muscle function during sleep in patients with chronic obstructive pulmonary disease (COPD)

3. Evaluation of sleep and sleep quality in COPD patients

Many patients with COPD experience nocturnal respiratory symptoms which interrupt sleep. When the frequency and severity of night symptoms increase, sleep quality decreases [26]. Sleep quality in patients with COPD is decreased both subjectively and objectively. Indicators

of poor sleep quality include the subjective complaints of difficulty falling and staying asleep, morning tiredness, early awakenings, and excessive daytime sleepiness [14,45, 46]. Cormick et al. asked patients with emphysema about their perception of sleep quality and found that 72% complained of daytime sleepiness, 32% reported impaired daytime concentration, and 28% complained of early morning headaches [14]. Sleeping problems seen in COPD patients are related to oxygen desaturation which occurs depending on the severity of the disease [37, 47]. During sleep, especially during REM, respiratory muscle function and the responsiveness of the respiratory centre to chemical stimulants decrease. Thus, COPD patients are at higher risk of developing nocturnal desaturation. Desaturation during sleep is considered a major determinant of disturbed sleep among COPD patients [48]. McSerry et al (2012) reported that sleep quality is poor in patients with severe COPD compared with individuals of similar age who do not have sleep apnea. Daytime hypoxaemia is independently associated with impaired sleep efficiency [49]. Kinsman et al. (1983) stated that disordered sleep is the third main complaint after dyspnoea and fatigue in patients with COPD and approximately half of the patients experience sleep disruption “always” or “generally always” [50]. Tel et al. (2006) determined that sleep quality is poor in patients with COPD and there is a significant relationship between the anxiety levels of patients and poor sleep quality [11]. Valipour et al. (2011) determined that compared with healthy people, patients with COPD experience more insomnia and sleep disorders [51].

Insomnia, nightmares, and somnolence are higher in patients with COPD than in the general population [52]. Nearly half of the patients with COPD stated that their quality of sleep was considerably impaired [37]. Valipour et al (2011) determined that insomnia, and sleep-maintenance difficulty occur frequently in patients with COPD [51]. Polysomnographic studies show that in patients with COPD, the sleep duration is shortened, arousals and awakenings occur frequently, and slow wave and REM sleep are shortened [14].

Poor quality of sleep in patients with COPD occurs as a result of many factors: age, severity of COPD, medications, underlying depression, and underlying sleep disorders [11,13,37,48]. George and Bayliff (2003) showed that the frequency of sleep disorders increases with the severity of the underlying pulmonary disease in COPD patients [41]. Pulmonary symptoms experienced by the patients also cause sleep disorders [53]. Omachi et al. (2012) found that sleep disorders are related to cough, dyspnoea and severity of illness in COPD patients. While many COPD patients suffer from the problem of excessive secretions, coughing to produce sputum/secretion results in interruptions in the sleep of the patients. Considering the sleep habits of the patients, most of them report that their sleep is frequently disrupted due to respiratory distress, cough and sputum production at night [54]. Using qualitative methods, Aydın Tel et al. (2012) showed that the majority of patients with COPD stated that their respiratory symptoms adversely affected their sleep [55].

Examples of patients' comments illustrating how their COPD affected their sleep include: Patient A *“Due to this disease, everything is problematic, including going to the toilet, having bath, dressing up, lying on the bed, sitting up and turning right and left. I become short of breath and I can do nothing.”*

Patient B, *"Sometimes I have a stuffed throat and become short of breath during sleep and then wake up by fluttering. I can never sleep on my back, I always lie laterally. I sleep while sitting and sometimes, I fall while sleeping."* [55]. Many COPD patients prefer to sleep in a chair instead of lying supine in order to ease breathing and improve sleeping. This way of sleeping pulls the diaphragm downwards and relaxes the respiratory mechanism [3]. Thus, COPD patients frequently prefer this position to sleep more comfortably and soundly.

Sleep disorders are also closely associated with the fatigue experienced by COPD patients. Patients with sleep disorders suffer from daytime chronic fatigue and lethargy and, therefore, their life quality is poorer [14, 56]. Poor sleep quality leads to various dysfunctions in COPD patients by causing daytime excessive sleepiness and changing neuro-cognitive and psychomotor wakefulness [25].

Although the exact impact of chronic sleep disorders on the pulmonary function of COPD patients is not known, interruptions in sleep may cause slight decreases in the forced vital capacity as well as at the forced expiratory volume in one second [57].

The most frequent sleep problems detected in patients with COPD are insomnia, waking up early in the morning, headache, and daytime sleepiness. Their prevalence varies between 30 % and 70 % in COPD patients [14, 45,52]. Klink et al. (1994) reported that 52.8% of COPD patients suffer from insomnia and daytime lethargy [58]. Subjective complaints related to sleep problems are accompanied by respiratory symptoms such as cough, dyspnoea, wheezing, and producing sputum [25]. Sleep disorders associated with COPD affect the quality of sleep deeply through multiple mechanisms. Omachi et al (2012) showed that sleep disorders experienced by COPD patients predict utilization of emergency services due to acute COPD exacerbations [54].

Successful COPD management requires consideration of all of the disease's effects on each person, not just from the perspective of COPD's main respiratory manifestations like dyspnoea, cough, and phlegm. Within this context, the relationship between pulmonary function and sleep shouldn't go unnoticed and a careful sleep history should be elicited from all patients with COPD. The first phase of effective disease management includes a diagnostic assessment of the patient and collecting the essential data to plan the treatment and care requirements accurately. Only successful disease management will eliminate the symptoms of COPD and improve a patient's clinical course. Hynnien et al. (2007) determined that anxiety, depression, and sleep disorders are associated with poor health perception by patients. According to their results, all patients should be assessed for anxiety, depression, sleep disorders, and daily functions irrespective of the severity/phase of their COPD [59]. Deficiencies in disease management result in the intensification of COPD symptoms, emergence of sleep disorders, significant changes in the cognitive functions, deterioration of the disease, and even death.

According to the results of the study conducted by Omachi et al. (2012), the relationship between sleep and pulmonary disorders in COPD patients is summarized in Figure 3 [54]. Seemingly, sleep disorders are experienced by all COPD patients and may lead to significant complications although their severities and intensities may be different. Thus, sleep habits of COPD patients and the factors affecting these habits should be assessed comprehensively [54].

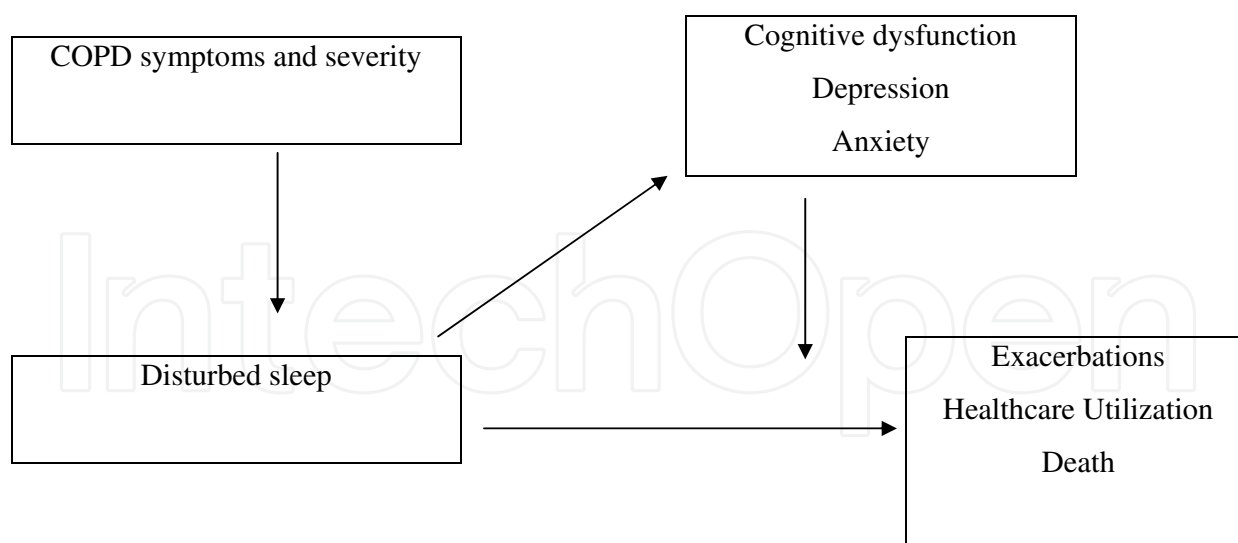


Figure 3. Omachi et al.(2012) Disturbed sleep among COPD patients is longitudinally associated with mortality and adverse COPD outcomes. *Sleep Med*, 2012, 13(5):476-483.

Most patients with COPD have poor sleep quality [11,36, 60,61]. Moreover, some studies suggest that in COPD patients, sleep quality is the most important health factor affecting quality of life. [36,62,63]. These results show that all COPD patients should be evaluated for symptoms of sleep disorders, snoring during sleep and potential sleep apnea syndrome symptoms like observable apneas [37]. In the clinical evaluation of COPD patients, questions to determine the sleep quality of patients and the potential existence of sleep apnea syndrome should be elicited.

Oxygen therapy, drug treatment, non-pharmacological approaches and sleep hygiene are the interventions recommended for COPD patients suffering from sleep disorders.

When discussing sleep problems in patients with COPD, the patient's respiratory symptoms should be discussed. Reduction in respiratory symptoms such as dyspnea and cough may be the initial management goals that will improve sleep quality [37]. When it is needed, nocturnal oxygen treatment should be provided and, as far as possible in patients with severe COPD, the use of hypnotics should be avoided [37]. The most important intervention is to prevent nocturnal hypoxemia [26]. Nocturnal oxygen treatment is suggested in cases of hypoxemia complications [37]. In a study of oxygen therapy on sleep quality Calverly et al. (1982) concluded that oxygen therapy increases REM sleep and sleep continuity and reduces sleep latency [64].

COPD medications may have varying effects on sleep quality. Theophylline [65] and anticholinergic medicines may ameliorate nocturnal desaturation and ipratropium increases sleep quality [66]. Ipratropium bromide enhances sleep quality, abrogates nocturnal oxygen desaturation, improves perceived sleep quality, and increases REM sleep duration without any effects on other sleep phases or total sleep duration [66]. On the other hand, while some studies examining the effect of Theophylline on sleep quality reported that it caused deterioration of sleep quality [65], other studies revealed that it had no effect on sleep quality [67-69].

Because of the potential negative effects of benzodiazepines on ventilation, these medicines should be avoided in patients with COPD [70]. It is recommended not to use benzodiazepines in the patients with COPD as they may exacerbate the frequency, duration, and severity of nocturnal hypoxemia [71].

In patients with COPD, treatments that improve lung function and gas exchange should improve sleep quality and overall health [72]. In COPD patients, good sleep quality also contributes to better overall health of patients [73]. Soler et al. (2013) showed that pulmonary rehabilitation is effective in improving the sleep quality of patients with COPD [74]. Increased awareness by medical professionals of the sleep problems of patients with COPD is important, since the sleep quality has an effect on patients' quality of life. In addition to treatment approaches that improve lung function and help the symptoms of the disease to be brought under control such as pulmonary rehabilitation, sleep and sleep hygiene education will help COPD patients acquire a high quality sleep pattern and increase their sleep quality.

Like patients with any chronic disease, patients with COPD who have perceptions of poor health are likely to experience anxiety, depression, sleep disturbance, and problems with daily functioning. Lee et al. (2011) suggested that these findings show the need to screen routinely for sleep disturbance in patients with COPD and support the potential benefits of interventions to enhance self-efficacy and quality of sleep in reducing depression in COPD patients [75].

There are some studies examining the effectiveness of pulmonary rehabilitation in eliminating sleep disorders in COPD patients. Soler et al. (2013) showed that pulmonary rehabilitation produced significant improvements in life quality perceptions of patients in relation to dyspnoea, exercise tolerance, self-effectiveness and health while 19% of the patients had improved/advanced sleep quality. Soler et al. (2013) suggested that pulmonary rehabilitation may be an effective, non-pharmacologic treatment option for sleep problems in patients with COPD [74].

Most of the patients with COPD suffering from sleep problems report a lack of support from their physicians and few received advice for sleep problems [13]. Sleep problems in patients with COPD may need specific evaluation [6]. Assessment of the sleep problems of patients with COPD is an issue that should not be ignored during routine care. Sleep characteristics of the patient should be assessed. The impact on sleep duration and quality can be recorded using validated tools such as the Pittsburgh Sleep Quality Index [76].

Another approach is to measure the emergence of daytime symptoms, such as day time sleepiness or fatigue, related to sleep deprivation. Daytime sleepiness can be assessed by the Epworth Sleepiness Scale [77]. The St George's Respiratory Questionnaire includes one question about sleep disturbance caused by cough or breathlessness [6]. For assessment of the impact of night-time symptoms and sleep disturbance in COPD, the COPD and Asthma Sleep Impact Scale may be used [78]. The patient should be informed adequately about all the processes in order to engage his/her participation in the practices aimed at solving the sleep problems. As stress and anxiety due to a lack of information will affect sleep, patients should be provided with adequate and timely information.

Restlessness, anxiety, confusion, and sleeplessness experienced by the patients with COPD are common symptoms of hypoxia and hypoxemia. To detect these symptoms, consciousness level and mental status of the patient should be monitored routinely. Supporting the positions that will ease the respiration of the patient and changing the position, if necessary, will help the patient breathe more comfortably. Patients with COPD frequently prefer sleeping in an upright position instead of lying on their back [53].

Encouraging and supporting the patients to produce sputum will facilitate clearance of secretions and ease breathing. To improve sleep quality of patients with COPD, health professionals can recommend some interventions such as maintaining a regular sleep and wake schedule, establishing a regular relaxing bedtime routine, restricting their activities in bed to sleep and sex, not for other stimulating activities, creating a sleep environment that is cool, dark, and comfortable and avoiding caffeine in the hours before bedtime.

4. Conclusion

Sleep, a physiological necessity, is important for all people in order to attain physical, psychological, and emotional wellness. However, in some situations, sleep may be stressful for patients especially those with COPD. Sleep disorders experienced by COPD patients adversely affect their sleep quality. Although patients with COPD frequently experience sleep problems and their sleep quality is unsatisfactory, healthcare providers do not review regularly their sleep characteristics and quality. The routine examination of patients with COPD should include a review of sleep symptoms and sleep quality to ascertain the effects of sleep disturbances on their lives. Only through the active assessment of a comprehensive sleep history can sleep disorders be diagnosed and managed. Healthcare personnel who provide holistic care will assess patients' sleep problems and symptoms. This approach will help to diagnose sleep problems early, initiate appropriate interventions and management, and improve patients' wellness.

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