Respiratory medications and sleep

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Abstract Respiratory physiology is affected by sleep. Patients with chronic lung disease often complain of poor sleep quality. Sleep disturbances may result from poor control of underlying lung disease, thereby disrupting sleep. Sleep disruption may result from hypoventilation resulting in worsened gas exchange. Sleep quality may also be affected by the respiratory medications used to treat certain lung diseases. These medications can have positive effects on sleep by providing better control of underlying respiratory abnormalities and therefore offering better sleep quality. These medications may also have undesirable side effects which can worsen sleep, such as hyperarousal resulting from corticosteroid use. Knowledge of medication effects on sleep is important in management of patients with underlying lung disease. As with all medications, it is important to balance potential benefits with possible negative side effects. This article discusses the effects of common medications used to treat respiratory diseases and their impact on sleep.

Keywords Respiratory medications · Sleep · Lung disease · Sleep disorder · Asthma · Bronchodilator · Corticosteroid

Introduction

Disturbed sleep is common in patients with chronic lung disease. Poor sleep quality may be due to a variety of causes, including nocturnal exacerbation of symptoms, worsening gas exchange due to reduced minute ventilation during sleep, or co-existing sleep-disordered breathing. Medications used to treat respiratory diseases have a variety of effects on sleep. Improved disease control may improve sleep quality by reducing respiratory disturbances during sleep. On the other hand, respiratory medications may also worsen sleep quality due to unintended side effects. Given the frequency of sleep complaints in patients with chronic lung disease, it is especially important to be familiar not only with the relationship between lung disease and sleep problems, but also the effects of respiratory medications on sleep.

Sleep and respiratory disease

Obstructive lung disease

Asthma

It has long been recognized that many patients with asthma experience worsening symptoms at night, a condition known as “nocturnal asthma.” This phenomenon is thought to be mainly due to circadian variations in airway caliber. It is known that even normal subjects demonstrate diurnal variation in peak expiratory flow (PEF), but an exaggerated response is seen in patients with nocturnal asthma [1]. Additional factors may include gastroesophageal reflux,

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airway cooling, and allergen exposure [2–4]. Obesity has also been associated with increased PEF variability [5]. Although the mechanism of this association is unclear, it has been increasingly recognized that sleep-disordered breathing is common in patients with difficult to control asthma [6].

Nocturnal asthma is often associated with poor asthma control during the day and increased morbidity, including reduced quality of life and increased sleep complaints. Patients with nocturnal asthma report worse sleep quality and demonstrate daytime cognitive deficits compared to normal subjects [7]. On polysomnography, children with asthma demonstrate increased awakenings and reduced sleep efficiency when compared to normal controls [8]. Sleep stage may also influence nocturnal asthma, with increased lower airways resistance seen during stage 3 sleep [9]. However, sleep disruption does not prevent circadian variability in peak flow [10].

COPD

Ventilation decreases during sleep in normal subjects, with the greatest fall seen during rapid eye movement (REM) sleep [11]. In patients with chronic obstruction pulmonary disease (COPD), this sleep-related hypoventilation can result in clinically significant nocturnal hypoxemia and hypercapnia [12, 13]. Patients with COPD also frequently report poor sleep, including increased sleep latency and nocturnal awakenings [14]. Multiple studies have demonstrated evidence of sleep fragmentation and frequent arousals on polysomnography [15, 16].

The term “overlap syndrome” has been used to describe co-existing COPD and obstructive sleep apnea (OSA). Patients with the overlap syndrome have more severe nocturnal hypoxemia, are at increased risk for pulmonary hypertension, and have worse sleep quality than with either condition alone [17]. The high prevalence of the overlap syndrome is likely due to the fact that both COPD and OSA are very common, and does not point to a shared pathophysiology [18].

Restrictive lung disease

Interstitial lung disease

Idiopathic pulmonary fibrosis (IPF) is the most common interstitial lung disease. Patients with IPF frequently report poor sleep quality and excessive daytime sleepiness [19]. Polysomnography in patients with IPF shows worsened sleep quality with increased stage 1 sleep and frequent arousals [20, 21]. Sleep fragmentation in IPF is associated

with awake hypoxemia [21]. Patients with IPF have a rapid, shallow breathing pattern during wakefulness. Sleep-related hypoventilation can occur, and may be associated with severe hypoxemia, but does not usually result in hypercapnia [22]. Little is known about sleep in non-IPF interstitial lung disease.

Kyphoscoliosis

Kyphoscoliosis is a condition in which there is abnormal curvature in both the lateral (scoliosis) and anteroposterior (kyphosis) dimensions of the spine. This may cause a restrictive ventilatory defect, and chronic respiratory failure can result. Not surprisingly, worsening hypoventilation during sleep, particularly in Stage REM, has been observed [23]. In addition, a wide spectrum of abnormal breathing patterns, ranging from central apneas to obstructive apneas and hypopneas, has been observed [24, 25]. The effect of other thoracic cage abnormalities on sleep is less well-known, but one study of 20 patients with restrictive lung disease after thoracoplasty reported modest oxygen desaturations during sleep [26].

Obesity

The link between obesity and OSA is well established. In addition, obesity can cause a restrictive ventilatory defect [27]. Daytime hypercapnia may be seen, termed the obesity-hypoventilation syndrome (OHS). Patients with OHS exhibit worsening hypercapnia during sleep, which may be due to recurrent upper airway obstruction from OSA, or sustained hypoventilation [28]. Even in the absence of sleep apnea, obesity is often associated with sleep disturbances, including short sleep duration and poor subjective sleep quality [29].

Cystic fibrosis

Cystic fibrosis (CF) is a common recessive genetic condition, affecting approximately 1/3,000 Caucasians in the United States. The pulmonary manifestations of CF include obstructive lung disease and chronic infection with bronchiectasis. Similar to other obstructive lung diseases, hypoxemia during sleep is commonly seen in CF [30]. Patients with CF also commonly report poor sleep quality, and disruptions in sleep architecture have been observed on polysomnography [30, 31]. There are several reported causes of disruption of sleep architecture in CF, including hypoxemia, cough, obstructive apneas, and pain [30, 32, 33]. Less is known about the impact of non-CF bronchiectasis, but one study of 54 children reported that poor sleep quality, frequent nocturnal respiratory symptoms, and obstructive sleep apnea were common [34].

Respiratory medications and sleep

It is well recognized that many medications can disturb sleep and wakefulness. This effect may be intentional, such as with sedative-hypnotics and stimulants, or may be an unintentional side effect. The neural regulation of sleep and wakefulness is complex, and a detailed discussion is outside the scope of this paper. However, a basic understanding of the neurotransmitters involved in sleep-wake regulation is essential to appreciate the mechanisms by which medications can disrupt sleep.

The neurotransmitters that promote wakefulness are a diverse group, with neuronal projections throughout the brain. These include glutamate, histamine, norepinephrine, dopamine, serotonin, acetylcholine, serotonin, and orexin. The main sleep-promoting neurotransmitters are GABA and adenosine. Extracellular adenosine concentrations in the basal forebrain increase during wakefulness and are decreased by sleep [35]. Interference with any of these sleep-related neurotransmitter systems, whether through receptor antagonism or reuptake inhibition, could cause alterations in the sleep-wake cycle [36].

Drugs that cross the blood–brain barrier and directly affect these neurotransmitter systems, for example antihistamines, are well recognized for their effects on sleep and wakefulness. Given the central role of neurotransmitters in sleep-wake regulation, it is not surprising that the most common medications to affect the sleep-wake cycle include medications for psychiatric and neurologic disease, such as antidepressants, antipsychotics, antiepileptic drugs, and medications for the treatment of Parkinson's disease [36].

Although some drugs that treat respiratory disease, such as corticosteroids, may cross the blood–brain barrier and directly affect sleep-wake regulation, the likely predominant mechanism by which respiratory medications affect sleep is through prevention of the adverse effects of respiratory disease itself. The exact mechanism of sleep disruption in respiratory disease is not understood, but hypoxemia, which is common to all advanced respiratory disease, may play an important role. Both intermittent and chronic hypoxemia are well known to have a significant and diverse effect on neurotransmitter synthesis in the central nervous system, including those involved in sleep-wake regulation [37•].

Oxygen

Although often not considered a true “medication,” long-term oxygen therapy is one of the few treatments that have been shown to improve survival in COPD [38]. However, nocturnal oxygen therapy has not been shown to have the same mortality benefits as continuous oxygen therapy [39]. There have been conflicting reports on the effect of nocturnal oxygen on sleep. In one study of 23 patients with COPD,

treatment with nocturnal oxygen did not result in improvements in sleep architecture or subjective sleep quality compared to compressed air [40]. However, in another study, supplemental oxygen improved sleep architecture in patients with COPD. Total sleep time was also improved in subjects with a low awake PaO₂ when they received supplemental oxygen [41]. In normal subjects at high altitudes, supplemental oxygen results in increased stage 3 and 4 sleep [42].

Beta agonists

Beta₂ adrenergic receptor antagonists are a common class of drugs used to treat obstructive lung disease. Drugs in this class include short-acting beta₂ agonists, such as albuterol, levalbuterol, terbutaline, and long-acting beta₂ agonists (LABA), such as formoterol and salmeterol. Indacaterol, an ultra-long-acting beta₂ agonist, was also recently introduced. Beta₂ agonists cause bronchial smooth muscle dilation, resulting in bronchodilation. As sympathomimetics, beta₂ agonists all have the potential to cause stimulant-like effects. Insomnia is a reported side effect of the beta₂ agonists.

The introduction of LABA therapy in the 1990s brought a new therapeutic option for patients with nocturnal asthma. Both salmeterol and formoterol were reported to improve subjective sleep quality in patients with asthma [43, 44]. There have been inconsistent results on the effects of LABA therapy on sleep architecture. In one study of 20 patients with stable, nocturnal asthma, salmeterol resulted in increased stage 4 sleep and reduced stage 1 and wake when compared to placebo [43]. However, in another study of 12 patients with stable COPD, salmeterol improved oxygen saturation during sleep, but had no effect on sleep architecture when compared to placebo [45•].

Anticholinergics

Inhaled anticholinergic medications are bronchodilators used in the management of COPD. Medications in this class include ipratropium bromide and the tiotropium, a long-acting agent. The mechanism of action is bronchial smooth muscle relaxation via binding to muscarinic receptors in the airways. The most common side effects, including dry mouth and urinary retention, are related to the anticholinergic activity. Since these medications are not sympathomimetics, they cause less stimulant effects compared to beta₂ agonists. For this reason, they are preferred for treatment in patients who have both COPD and insomnia [14].

It has been suggested that circadian variability in cholinergic tone may contribute to the disrupted sleep and nocturnal hypoxemia that has been observed in patients with obstructive lung disease [46]. In 36 patients with moderate

to severe COPD, a 4-week treatment with ipratropium bromide nebulized four times daily resulted in improved subjective sleep quality and a significant increase in REM sleep when compared to placebo [46]. In a study of 80 patients treated with daily tiotropium (AM or PM dosing) or placebo, there was improvements in oxygen saturations during sleep with tiotropium, but no change in quality of sleep as measured by polysomnography and subjective symptoms [47].

Corticosteroids

Corticosteroids are administered via multiple different routes (intravenous, oral, inhaled, nasal) for both acute exacerbations and chronic maintenance therapy of chronic respiratory disease. The data on the effect of corticosteroids on sleep is variable, owing to the number of different preparations studied in a wide variety of disease conditions. Much of the existing data on the effects of systemic corticosteroids on sleep is from use in non-respiratory diseases, such as auto-immune disease and chemotherapy. In addition, most studies are limited to dexamethasone and hydrocortisone, which are not commonly used in treatment of respiratory disorders.

In normal subjects, dexamethasone increases sleep latency and alertness when given prior to sleep [48]. Both hydrocortisone and dexamethasone reduce REM sleep and increase nocturnal awakenings, but dexamethasone decreases slow-wave sleep, whereas hydrocortisone increases slow-wave sleep [49]. In clinical use, oral corticosteroids commonly cause insomnia, an effect that seems to be dose-related [50]. In stable COPD patients with nocturnal hypoxemia, a course of methylprednisolone has been shown to improve mean oxygen saturation during sleep as well as sleep duration [51].

Inhaled corticosteroids reduce the nocturnal drop in forced expiratory volume (FEV1) in nocturnal asthma [52]. When used as a controller medication in asthma, patients report improvement in nocturnal symptoms [53]. Inhaled corticosteroids do have some systemic absorption, and exhibit dose-related adrenal suppression [54]. It is not known whether inhaled corticosteroids affect sleep architecture like systemic corticosteroids. However, insomnia and sleep disorders are reported side effects of several inhaled corticosteroids [55–57]. It has also recently been reported that there is a dose-dependent association between inhaled corticosteroid use and symptoms of sleep apnea in asthmatic, but it is not known whether this is a causal relationship [58••].

Nasal steroids are used in the management of allergic rhinitis, which is commonly associated with asthma [59]. It has been well documented that allergic rhinitis can be associated with poor subjective sleep quality and symptoms of

excessive daytime fatigue [60]. Polysomnography in patients with persistent allergic rhinitis demonstrates decreased sleep efficiency, increased arousals, reduced oxygen saturations, and increased snoring (with no difference in apnea-hypopnea index) when compared to controls [61]. Treatment with nasal steroids improved subjective sleep quality and daytime symptoms [62].

Montelukast

Montelukast is a leukotriene receptor antagonist approved for treatment of asthma, exercise-induced bronchoconstriction, and allergic rhinitis. When used as add-on therapy for uncontrolled asthma, improvements in nocturnal awakenings and subjective sleep quality have been reported [63]. However, when compared to inhaled fluticasone for the maintenance treatment of persistent asthma, montelukast was found to be less effective than inhaled fluticasone in improving nocturnal awakenings and other measures of asthma control [64]. Montelukast has also been shown to improve subjective sleep quality and daytime sleepiness when used to treat allergic rhinitis [65]. However, in post-marketing surveillance, insomnia, drowsiness, and dream abnormalities have all been reported [66].

A novel use of montelukast in the treatment of childhood OSA has also recently been described. Adenotonsillar hypertrophy plays a critical role in the pathogenesis of OSA in children, and adenotonsillectomy is the first-line treatment. It has been reported that there is increased expression of leukotriene receptors in adenotonsillar tissue of children with OSA [67]. In clinical trials, montelukast was effective in improving sleep-disordered breathing as both a first-line therapy for mild OSA and as a second-line treatment (in combination with nasal steroids) for residual OSA after adenotonsillectomy [68, 69].

Theophylline

Theophylline is a methylxanthine with bronchodilator properties used in the treatment of asthma and COPD. Methylxanthines, which also include caffeine, are adenosine receptor antagonists. Thus, it is not surprising that theophylline has multiple effects on sleep. In normal subjects, theophylline administration increases sleep latency and increases wake and stage 1 sleep [70]. However, the adverse effects of theophylline on sleep may be offset by its therapeutic action when used in patients with chronic lung disease. In patients with COPD, a higher serum theophylline concentration improved nocturnal respiratory function without impacting sleep architecture [71]. Of note, circadian variability in theophylline absorption has been described and special attention is required to the timing of doses to ensure adequate nocturnal serum levels [72].

Theophylline has also been used in the treatment of sleep-disordered breathing, including central and obstructive sleep apnea. Theophylline is commonly used to treat apnea of prematurity and periodic breathing in infants. In adults, theophylline has been effective in improving central sleep apnea with periodic breathing in patients with chronic heart failure, although the mechanism is unclear [73]. A similar effect is seen with theophylline treatment for periodic breathing during sleep at high altitude [74]. Theophylline has also been studied in obstructive sleep apnea, where it has been reported to produce slight reductions in obstructive apneas, but at the expense of increased sleep fragmentation [75].

Antibiotics

Antibiotics are widely used in the management of patients with chronic lung disease, both for short-term treatment of infectious exacerbations and long-term suppression of chronic pulmonary infections. There is little data on the therapeutic benefit of antibiotics in reducing sleep disturbances in chronic lung disease. One large non-controlled trial of use of moxifloxacin in acute exacerbations of chronic bronchitis reported reduction in sleep disturbances during treatment with moxifloxacin [76]. However, quinolone antibiotics have also been associated with a number of adverse sleep-related side effects as well. Ciprofloxacin has been reported to cause nightmares [77]. Fleroxacin, which is no longer on the market in the United States, was also reported to frequently cause insomnia [78]. Macrolide antibiotics, which are used in respiratory disease to treat infections and for their anti-inflammatory effect, have also been reported to cause sleep disturbances. There is a case report of erythromycin as a cause of nightmares [78]. Two cases of hypersomnia secondary to clarithromycin have also been reported [79].

Inhaled antibiotics are becoming increasingly popular in the management of chronic pulmonary infection; however there is no data regarding their effect on sleep. In one case series of three children with CF who developed severe sleep disturbances (nightmares, insomnia) while being treated with inhaled colistin and oral ofloxacin, symptoms improved when the children's medication was changed to a different oral quinolone and were not thought to be related to inhaled colistin [80].

Immunosuppressants

Immunosuppressant medications may be used in selected cases of interstitial lung disease and after lung transplantation. There is little data on the effect of immunosuppression on sleep in patients with chronic lung disease. Methotrexate is known to cause neurotoxicity that may manifest with

increased sleepiness. Interestingly, this syndrome is thought to be mediated by adenosine release in the CNS, and is improved with treatment with aminophylline, a methylxanthine that acts as an adenosine receptor antagonist [81]. This reaction is more commonly reported after intrathecal methotrexate therapy, but excessive daytime sleepiness has also been reported with low-dose oral methotrexate therapy as well [82]. Insomnia is a frequently reported side-effect of tacrolimus [83]. There are no sleep-related side effects reported for azathioprine and cyclophosphamide [84, 85].

Omalizumab

Omalizumab is a humanized anti-IgE monoclonal antibody used in the treatment of allergic asthma. In one study, patients receiving omalizumab had significantly fewer sleep disturbances compared to patients on salmeterol/fluticasone combination therapy [86]. Two studies of omalizumab as add-on therapy in moderate to severe asthma also demonstrated improvement in nocturnal asthma symptoms [87, 88].

Dornase alpha

Dornase alpha is an inhaled recombinant human DNase approved for use in cystic fibrosis to improve lung function. It acts by cleaving DNA in mucous, resulting in reduced mucous viscosity. Use of dornase alpha may result in modest improvements in health-related quality of life [89]. There are few data on the effect of dornase alpha on sleep in CF, but one small study in CF patients younger than 5 years reported improved subjective sleep quality when compared to placebo [90].

Roflumilast

Roflumilast is a phosphodiesterase-4 inhibitor recently approved to reduce the risk of COPD exacerbations in patients with severe COPD. Insomnia is reported to be a common adverse side effect of this medication [91]. There are no data yet on the effect of roflumilast on sleep quality in patients with COPD.

Conclusions

Sleep is a complex process involving neurotransmitters and neural pathways with physiologic effects on various organ systems. Respiratory physiology is altered during sleep, which can result in hypoventilation, hypoxemia, and worsening of underlying respiratory disease. Sleep disruption and nocturnal hypoxemia are common in patients with chronic lung disease. Respiratory medications may improve

disease control and alleviate nocturnal symptoms. However, these same medications may have unintended side effects that may interfere with normal sleep. Therefore, it is important to balance the benefits of these respiratory medications with any potential adverse effects. Knowledge of the complex interaction between pulmonary disease, sleep quality, and respiratory medications may help improve sleep and quality of life in patients with chronic lung disease.

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