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Review Article

Hypnotic use for insomnia management in chronic obstructive pulmonary disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality and morbidity worldwide. Because of the chronic nature of the disease, optimal care for patients includes successful treatment of comorbidities that accompany COPD, including insomnia. Insomnia symptoms and associated disruption of sleep are prevalent in COPD patients but treatment with traditional benzodiazepines may compromise respiratory function. This review summarizes the efficacy and safety consideration of current drugs available for the treatment of insomnia in COPD patients including benzodiazepines, non-benzodiazepine receptor agonists such as eszopiclone, zolpidem, and zaleplon, sedating antidepressants such as trazodone, and the melatonin receptor agonist ramelteon.
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1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) encompasses a range of respiratory diseases including chronic bronchitis, emphysema, and others. The disease is defined as a progressive limitation of functional airflow that is not fully reversible with inhaled bronchodilators [1]. The disease is progressive and chronic, requiring long-term treatment to improve quality of life in affected patients.

Several comorbidities accompany COPD including unexplained weight loss, cardiovascular disease, peripheral muscle weakness, cognitive impairment, depression, anxiety, and sleep disorders [2,3]. COPD patients are more likely to have difficulty falling and staying asleep and have increased sleepiness during the day. In some cases, they take hypnotics to combat their sleep disturbance. Arousals from sleep are more likely in these patients due to chronic coughing and nocturnal wheezing and also nocturnal oxygen desaturation [4]. In addition, an increased number of COPD patients also have obstructive sleep apnea syndrome (OSAS), a condition that is referred to as overlap syndrome [5]. The coincidence of OSAS has detrimental effects on respiratory physiology and exacerbates hypoxia and hypercapnia in COPD patients during sleep [6]. This is particularly important to recognize because hypoxia correlates strongly with nocturnal mortality [7].

The most common pharmacologic treatment prescribed for insomnia including those comorbid with COPD are the benzodiazepine receptor agonists (BZRAs), a group of drugs that function by binding to the benzodiazepine receptor at the $GABA_A$ complex. These receptors are expressed in the plasma membrane of neurons throughout the CNS and PNS [8]. BZRAs include both the traditional benzodiazepines, which bind a broad range of BZ receptors and a newer group of more selective BZRAs called the non-benzodiazepine BZRAs. These drugs are more selective to a BZ receptor

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subtype that is expressed in the CNS and people have hypothesized that they produce fewer adverse side effects on pulmonary function than do the traditional BZRAs [8]. The selective MT_1/MT_2 melatonin receptor agonist ramelteon is another option for the treatment of insomnia. Melatonin receptors, expressed in the hypothalamus, regulate neural and endocrine mediated processes that control mammalian circadian rhythms [9]. By engaging signaling pathways downstream of these G-protein coupled receptors, ramelteon is believed to decrease sleep latency and increase sleep efficiency. Finally, the antidepressant trazodone is sometimes used off-label for treatment of insomnia and may be considered for use in COPD patients, although there is a lack of data on its effectiveness and safety in this patient population (NIH consensus statement).

It has become clear that the COPD patient population comorbid for insomnia is underserved by current practices in sedative pharmacotherapy. The current treatment paradigm relies heavily on CNS depressants, namely benzodiazepines, that can lead to hypoxia [4]. While there are no pharmacological treatments specifically indicated for the treatment of sleep disturbances in the COPD population, evidence suggests a reevaluation of the current treatment paradigm for this cohort of patients. As our understanding of sleep mechanisms has increased, so too has our appreciation for the clinical potential associated with newer sleep therapies. This review will discuss the clinical impact of insomnia on the COPD population and will highlight special considerations to be taken for this population and the risks related to current pharmacological treatment options of insomnia in COPD.

2. Effects of sleep on respiratory function in the COPD population

During sleep, a number of respiratory functions are affected in normal healthy individuals, including alterations in central respiratory control, airway resistance and airway muscle tone. Overall, these effects result in hypoventilation, moderate hypercapnia, and hypoxia [10]. During sleep the response of the respiratory center in the brain to both hypoxia and hypercapnia is attenuated, particularly during phasic REM sleep [11–13]. The changes in arterial blood gases that occur in normal subjects during sleep are exacerbated in patients with COPD. Moreover, sleep related breathing disorders occur with relatively high frequency in this population, further worsening sleep-related hypoxia and hypercapnia, particularly during REM sleep [14]. These alterations in COPD patients may contribute to an increased frequency of nocturnal awakenings. In addition, these effects of sleep on blood gas levels should be taken into consideration when choosing hypnotic treatment for insomnia, as those that promote further alterations may be particularly dangerous in this patient population.

Patients with COPD have varied levels of alterations in arterial blood gas values during wakefulness. Those that exhibit even mildly hypoxic diurnal arterial oxygen tension (P_aO_2) levels tend to develop substantial nocturnal oxygen desaturation, especially during REM sleep [14]. Studies have recognized that the hypoventilation that occurs during sleep is the major cause of nocturnal oxygen desaturation among COPD patients [4,15,16]. Furthermore, the changes in respiratory muscle function that occur during sleep, worsen functional residual capacity and contribute to lower ventilation/perfusion matching, exacerbating desaturation [17,18]. Nocturnal P_aO_2 tends to be lower in COPD patients relative to normal subjects since the P_aO_2 drops observed normally during sleep cause a larger drop in saturation when the patient is already hypoxemic, following the steepness of the oxyhemoglobin dissociation curve [3,19].

Obstructive Sleep Apnea Syndrome (OSAS), relatively common in individuals over the age of 45, occurs in about 10–15% of patients with COPD, a condition referred to as "Overlap Syndrome" [20]. Individuals with both conditions tend to develop dangerously low levels of P_aO_2 which is believed to occur because COPD patients are already hypoxemic at the beginning of each apneic event [20–22]. Alterations in arterial blood gas values in individuals with Overlap Syndrome lead to pulmonary hypertension which is associated with increased risk of cardiac arrhythmias and cor-pulmonale. These patients have a decreased survival rate over 5 years relative to patients that have OSAS alone [23].

3. Insomnia in the COPD population

Nocturnal hypoxia and hypercapnia cause increased arousals and sleep disruption in COPD patients to improve respiration. This leads to sleep disruption and, in vulnerable individuals, chronic insomnia [3]. Over 50% of COPD patients report a long sleep latency, frequent arousals during the night and/or general insomnia [8]. Insomnia tends to be more prevalent and severe with advanced disease, roughly correlating with the extent of underlying lung disease [24]. Analysis of a large COPD database revealed that 21.4% of the listed COPD patients were diagnosed with and were treated for insomnia as compared to only 7.2% of non-COPD patients [25].

4. The effects of COPD treatment on the development of insomnia

Although few studies have been done to determine the role that drugs used to treat COPD have on sleep, it is clear that insomnia can be a side effect of some of these medications. For example, bronchodilators used

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