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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.

Keywords: Drug therapy; Respiratory diseases; Sleep disorders; Insomnia; Chronic Obstructive Pulmonary Disease; Hypnotics

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

to treat some COPD patients have been noted to cause insomnia in a small population of treated patients [26–28]. In addition, other medications commonly prescribed to COPD patients including corticosteroids and β-adrenoreceptor agonists contribute to insomnia [29]. In contrast, nocturnal oxygen therapy has been shown to improve sleeplessness in COPD patients, perhaps by preventing awakenings due to oxygen desaturation during the night [30]. There is a lack of studies done to determine whether or not expectorants have any impact on the quality of sleep in COPD patients.

5. Pharmacologic treatment of insomnia

There are currently a limited number of classes of medication that are used to treat insomnia (Table 1). Benzodiazepine receptor agonists (BZRAs) are the most commonly prescribed sleep agents used in the management of insomnia in the COPD population [8,31,32]. This class of drugs includes both the traditional benzodiazepines that share the formal benzodiazepine chemical structure and have affinities for multiple subtypes of BZ receptors as well as the newer non-benzodiazepines (zolpidem, eszopiclone, and zaleplon), that have a higher selectivity for a narrower range of BZ receptor subtypes [33]. Another treatment option for insomnia in COPD patients is ramelteon, a MT_1/MT_2 melatonin receptor agonist [9]. In clinical trails, ramelteon has been shown to be safe in patients with mild-to-moderate COPD and in mild-to-moderate OSAS patients [34,35]. Finally, low dose sedating antidepressants such as trazodone have been used as an off-label treatment of insomnia. However, it is not clearly understood at what doses these drugs promote sleep and the safety of these doses. Clinical studies have found this agent to be safe in not exacerbating respiratory function in COPD patients, but there is no data on dose related safety and efficacy in subjects not suffering from depression [31,32,36].

6. Complications associated with the use of standard insomnia treatment

6.1. Traditional benzodiazepines

The benzodiazepines traditionally prescribed for insomnia include those indicated specifically for insomnia, namely, temazepam, triazolam, flurazepam, estazolam, and quazepam among others (Table 1) [33]. These drugs have varied half-lives and some result in the production of active metabolites which cause daytime impairment. Those with shorter half-lives that do not result in the production of active metabolites are most useful in elderly patients and significantly decrease sleep latency but have less of an effect on sleep maintenance against which intermediate acting drugs are more effective. Longer acting benzodiazepines lead to residual cognitive effects the following day [33].

When used in normal subjects, few significant adverse side effects on pulmonary function have been observed with benzodiazepines. However, despite being commonly used in the treatment of insomnia in COPD patients, several reports describe adverse pulmonary events associated with benzodiazepine usage in these patients. Some trials have reported adverse effects on pulmonary function in patients with COPD. In one small study on the effects of 1.5–2 mg dose of lorazepam on respiratory function in COPD patients, the authors noted a 20% decrease in minute ventilation due to decreased tidal volume. In addition, they observed a 10–15% reduction in a number of respiratory muscle functional parameters after a single dose, including negative effects on diaphragmatic endurance [37]. In another study, it was found that a 30 mg dose of flurazepam resulted in a decreased tidal volume in mild COPD patients, and a decrease in oxygen saturation [38]. Beaupre et al. reported that administration of a single oral dose of diazepam to patients with moderate to severe

Table 1
Pharmacologic options for treatment of insomnia

Drug classification	Drug subclass	Drug(s) (half-life)	Receptor	Mechanism of sedation
BZRA[a]	Benzodiazepines	Lorazepam (10–12 h) Temazepam (8–20 h) Triazolam (2 h) Flurazepam (>40 h) Estazolam (10–24 h) Quazepam (25–100 h)	BZ_1, BZ_2, BZ_3, BZ_5	Neuron desensitization, CNS depression, smooth muscle relaxation, anxiolytic effects
BZRA[a]	Non-benzodiazepines	Zopliclone (5–6 h) Eszopliclone (5–6 h) Zolpidem (2 h) Zaleplon (2 h)	$BZ_{1,3}$	Neuron desensitization, CNS depression
Antidepressants	Serotonin reuptake receptor antagonist	Trazodone (3–6 h)	$5HT_{2A}$ serotonin receptors	Unknown, may indirectly ↑ GABA levels
Melatonin receptor agonists	Selective MT_1/MT_2 receptor agonist	Ramelteon (1–2 h)	MT_1/MT_2	Blocks circadian alerting signals in the hypothalamus

[a] Benzodiazepine receptor agonist.

COPD resulted in a significant decrease in ventilatory drive in response to hypercapnia and mouth occlusion [39]. Another study found that 0.25 mg triazolam significantly increased the arousal threshold to airway occlusion and in both normal subjects and those with severe OSAS [40,41]. Thus, benzodiazepines depress respiratory functions that participate in maintaining homeostasis of arterial blood gases during sleep.

It is recognized that different BZ receptor subtypes mediate different effects. Benzodiazepines are thought to produce sedative effects through BZ_1 receptors and anxiolytic and other effects through BZ_2 and BZ_3 receptor subtypes [42,43]. However, apart from binding receptors in the CNS, benzodiazepines also have effects on neurons to peripheral tissues. Benzodiazepines inhibit voltage-gated Ca^{2+} channels in canine tracheal smooth muscle cells, leading to pulmonary muscle relaxation, although this effect is not blocked using $GABA_A$ receptor antagonists, suggesting alternative pathways [44]. In addition, they inhibit nerves that control the upper airway muscles. It is recognized that inhibition of the hypoglossal nerve and the recurrent laryngeal nerve by benzodiazepines can lead to airway obstruction during sleep [42,43].

Altogether, these observed effects on respiratory function suggest that there are significant safety concerns associated with the use of benzodiazepines in the COPD population. These risks are heightened further in patients with Overlap Syndrome who are already hypoxic at the start of apneic episodes. In addition, adverse effects of benzodiazepines on cognitive function suggest that they may not be the best choice for use in elderly COPD patients who may be at increased risk for falls and fractures.

6.2. Non-benzodiazepine BZRAs

A newer generation of BZ receptor agonists, also known as non-benzodiazepines, has a higher selectivity for BZ receptor subtypes expressed predominantly in neurons of the CNS (Table 1). These drugs have little to no affinity for the other $GABA_A$ receptor subtypes, and have fewer adverse effects on respiratory function than do the traditional benzodiazepines. Furthermore, these drugs specifically target the receptor believed to mediate the sedation effects of the BZRAs [45]. Drugs in this subclass include zolpidem, zolpdem CR, zopiclone and its active racemate eszopiclone, and zaleplon (Table 1). While zolpidem and zaleplon show selectivity for the BZ alpha 1 subunit, zopiclone and eszopiclone are selective for the alpha 3 subunit.

The non-benzodiazepine BZRAs have similar effects on sleep latency and efficiency as traditional benzodiazepines (Table 2) [33]. Several clinical studies have been conducted to test the effects of these drugs on pulmonary function. Unlike benzodiazepines, zopiclone (7.5–10 mg) and zolpidem (10 mg) have been found to have no significant effect on ventilatory drive and central control of breathing in normal subjects or in patients with mild to moderate COPD [39,46–48]. One small study has noted a non-significant trend towards an increased number and duration of apneic spells in patients taking 5–10 mg zopiclone [49].

Furthermore, non-benzodiazepine BZRAs have amnestic and cognitive effects similar to benzodiazepines. A recent review reported sixteen studies that included 1541 participants that evaluated the differences between benzodiazepines and non-benzodiazepines in terms of cognitive and psychomotor adverse events in elderly patients over the age of 60 years, finding no significant differences between treatments [50]. Thus, although non-benzodiazepines have fewer apparent adverse effects on pulmonary function, the potential for adverse effects on cognitive function may complicate treatment of insomnia in COPD patients, many of whom suffer from cognitive impairment or are elderly patients at risk for fall-related fractures [51].

6.3. Ramelteon

Ramelteon is a MT_1/MT_2 melatonin receptor agonist and thus mediates similar action to the endogenously produced hormone, melatonin, by decreasing sleep latency [9]. Ramelteon has no known appreciable affinity for the benzodiazepine or any receptor at the $GABA_A$ complex or receptors that bind neuropeptides, cytokines, serotonin, dopamine, noradrenaline, or opiates [52]. In contrast to melatonin, ramelteon has no affinity for the MT_3 receptor which may mediate other functions of melatonin on the gastrointestinal system. MT_1 and MT_2 receptors are expressed in the hypothalamus and respond to the hormone melatonin that is released by the pineal gland in response to photoreceptor signals. Melatonin levels are highest during periods of darkness and are believed to promote drowsiness in humans through poorly understood mechanisms. In animal studies and human clinical trials, ramelteon promotes similar effects, in particular a significant reduction in latency to persistent sleep and an increase in total sleep time in normal subjects [53–55].

While more clinical trials need to be done to assess the effects of ramelteon on respiratory function, three studies have recently been conducted. In a randomized study, ramelteon was demonstrated to be safe in patients with mild-to-moderate COPD, and the group receiving the drug did not exhibit differences in nocturnal P_aO_2 [34]. This point is important because hypoxia correlates with nocturnal mortality in patients with COPD and may also lead to increased awakenings [4,7]. In addition, there was no effect of ramelteon treatment on the apnea/hypopnea index, and ramelteon has been shown to be safe in patients with mild to moderate OSAS [34,35].

Table 2
Known adverse effects of current pharmaceuticals on respiratory function in COPD patients

Drug subclass	Effects on sleep	Adverse pulmonary effects in COPD patients	References
Benzodiazepines	↓ sleep latency, ↑ sleep efficiency, ↓ arousals	↓ tidal volume, ↓ arousal response to hypercapnia, ↑ hypoxia, ↑ hypercapnia	[37–39]
Non-benzodiazepines	↓ sleep latency, ↑ sleep efficiency, ↓ arousals	↑ apneas[a]	[49]
Melatonin receptor agonists (ramelteon)	↓ sleep latency, ↑ sleep efficiency	No effect on apnea or P_aO_2[a]	[56]
Trazodone	↑ sleep efficiency (only in patients with depression)	Unknown[a]	[58]

[a] Further research is needed.

A recent double-blind placebo-controlled study was the first study to test the effects of ramelteon on oxygen saturation in moderate to severe COPD patients [56]. Patients in the ramelteon treatment group had similar mean nocturnal PaO_2 levels as those who received placebo. In addition the patients who took ramelteon exhibited a significant increase in total sleep time and efficiency. Another advantage of ramelteon is that it does not appear to have adverse effects on cognitive function, which is particularly important in treating COPD and elderly patients.

6.4. Trazodone

Trazodone is a commonly prescribed antidepressant commonly administered to non-depressed patients as an off-label treatment for insomnia (Table 1) [36]. Though trazodone is known to act as a serotonin reuptake receptor (5-HT_2) antagonist, the exact mechanism behind its effects on sleep promotion remains unclear [57]. Serotonin neurotransmitters act on these G-protein coupled receptors expressed in neurons of the CNS and smooth muscle cells. Trazodone may indirectly lead to increased GABA release as a result of increased levels of serotonin, but it is still unclear if this is how it mediates its sedative effects [57] and, more importantly, at what dose and with what safety cost.

The data on the effectiveness of trazodone in normal subjects is limited and there are virtually no studies done in patients with COPD. Very little data suggest that trazodone improves sleep in patients without a mood disorder [58]. Furthermore, there is no dose–response data for trazodone on sleep and safety at hypnotic doses to date, and available data suggest tolerance occurs to its hypnotic effects. There is also a lack in clinical trial data on the effect of trazodone on respiratory function. It should also be noted that trazodone has been reported to be associated with cardiac arrhythmias [58]. Adverse effects observed with trazodone in normal patients include cognitive impairment, dizziness, and psychomotor difficulties [59].

Because meaningful clinical research of the effects of trazodone on respiratory function and in COPD patients has not been done, the off-label use of this drug to treat insomnia in these patients should be reconsidered, even in patients who do have a mood disorder. Moreover, the adverse effects of trazodone on cognitive function may create special challenges in the COPD population due to the prevalent cognitive dysfunction that is comorbid in COPD patients [51].

7. Conclusion

COPD is a leading cause of worldwide mortality. Managing quality of life in COPD patients is critical as they are likely to live with the disease as it progresses over significant periods of time. Among other comorbidities, insomnia is prevalent in the COPD population and affected individuals seek treatment to improve their quality of sleep. Additionally, a significant percentage of COPD patients also have OSAS, which further complicates treatment of sleep disorders in the COPD population [4,20,22]. The natural drops in minute ventilation, tidal volume and functional residual capacity, coupled with the increased airway resistance and respiratory muscle atonia that occur normally during sleep, exacerbate the hypoxia and hypercapnia seen in COPD, producing nocturnal oxygen desaturation in this population [17,60]. These changes in arterial blood gases and reduced pulmonary muscle strength and endurance increase the risk of nocturnal mortality [14,61].

Safe pharmacological treatment of insomnia must include consideration for whether the hypnotic could potentially exacerbate the already impaired gas exchange and atonia problems that present during sleep in COPD patients. Benzodiazepines are prescribed despite adverse pulmonary effects that could potentially lead to poor outcomes in the COPD population [8,62]. Furthermore, the side effects of cognitive impairment and anterograde amnesia make benzodiazepines a poor choice for the elderly COPD population. These complications highlight the need to reevaluate the current insomnia treatment paradigm in the COPD population.

The non-benzodiazepine BZRAs may offer some benefit in comparison to traditional benzodiazepines with respect to respiratory depression complications. However, there is some data to suggest that these drugs may promote apnea, which is known to significantly exacerbate hypoxia in COPD patients. Both types of BZRAs have amnestic effects which may pose problems if prescribed in the elderly COPD population already predisposed to cognitive impairment [32,63]. Ramelteon shows promise in the COPD patient suffering from insomnia. It has been determined to be safe and efficacious in mild to moderate COPD and OSAS patients, with no adverse effects on nocturnal arterial blood gases [34,35], however more clinical research needs to be done with ramelteon in this population. Trazodone has been shown to be effective only in patients with depression and comorbid insomnia. In addition, there is little to no data on the effects of trazodone on pulmonary function or in patients with COPD and OSAS [36,58,59]. While evidence and opinion point to a reevaluation of traditional BZRA therapies in favor of newer agents for COPD comorbid with insomnia, more research is needed to determine the safest and most effective treatment strategies.

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