Therapies for Insomnia and Comorbid Chronic Obstructive Pulmonary Disease With a Focus on Ramelteon (Rozerem)

Jack Greenberg, MD, and J. B. Goss, RPh, PhD

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent medical condition in the U.S., affecting almost 24 million adults. Approximately half of these cases remain undiagnosed. COPD and allied conditions are the fourth leading cause of death in the U.S., with more than 120,000 deaths having been reported in 2004. Each year, approximately 726,000 hospitalizations, 1.5 million emergency department (ED) visits, and 8 million physician visits are associated with COPD. COPD is more prevalent among people 65 years of age and older and affects 10% of individuals in this age group. With the proportion of Americans 65 years of age and older expected to increase from 12.4% in 2005 to 20.7% in 2050, the burden of COPD on the U.S. health care system also is expected to increase.

In 2007, COPD was associated with $42.6 billion in direct and indirect costs. The $26.7 billion in direct costs included $11.3 billion for hospital care, $6.2 billion for prescription drugs, $4.9 billion for physician services, $3.3 billion for nursing-home care, and $1.0 billion for home health care. The remaining $15.9 billion was attributed to lost productivity resulting from excess morbidity ($8 billion) and mortality ($7.9 billion). COPD has also had a detrimental effect on patients’ quality of life, often resulting in poor physical functioning, an inability to work, and depression. According to one survey, 34% of patients reported that they were prevented from working because of COPD, and among patients of working age with COPD, an average of 18.7 days of work were missed during the preceding year.

Thus, with the expected increase in the elderly population over the next 20 years, the prevalence of COPD is expected to rise. It is already well established that the prevalence of insomnia is higher among older adults and that its management and treatment is especially challenging in this population because of multiple comorbidities, polypharmacy, and safety concerns. Therefore, special considerations are needed to ensure optimal outcomes while minimizing the potential for adverse events, especially among patients with impaired lung function.

Our article reviews the relationship between COPD and insomnia, as well as nonpharmacological and pharmacological management strategies. We emphasize the benzodiazepines, the non-benzodiazepines, and a melatonin receptor agonist, ramelteon (Rozerem, Takeda). In researching this topic, we conducted a PubMed literature search using the terms hypnotics and sedatives; insomnia; sleep disorders; pulmonary disease, chronic obstructive; and ramelteon. Our search included all studies conducted between January 1996 and September 2008. We then supplemented the clinical literature according to an analysis of the references collected from the original literature search.

ASSOCIATION BETWEEN SLEEP-RELATED DISORDERS AND PULMONARY DISEASE

Patients with COPD often have a high prevalence of sleep-related problems. In a survey of 2,187 participants in the Tucson Epidemiologic Study of Obstructive Airways Disease, more than 50% of patients with COPD complained of difficulty initiating or maintaining sleep and more than 25% reported excessive daytime sleepiness. COPD was defined as either chronic bronchitis alone, chronic bronchitis with asthma, or emphysema. These rates were significantly higher compared with those in patients without respiratory disease. Only 36% of non-COPD patients reported difficulty initiating or maintaining sleep, and fewer than 11% reported excessive daytime sleepiness.

In another survey, insomnia was the third most common comorbidity reported by patients with chronic airway obstruction, after locomotive diseases (rheumatoid arthritis, arthritis, slipped disc, a back disorder lasting for more than three months), and hypertension. After we adjusted for differences in age, sex, and insurance coverage, these patients were 1.65-fold more likely to have insomnia than controls without respiratory disease. Similarly, sleep-related complaints were ranked as the third most common symptom category, behind dyspnea and fatigue, in COPD patients. Among patients with COPD, insomnia had an adverse effect on health-related quality of life compared with COPD patients with no comorbid conditions. COPD patients experience a delayed onset of sleep, increased nighttime arousals and awakenings, and poorer sleep efficiency compared with individuals without COPD. The degree of disturbance corresponded roughly with the severity of pulmonary disease. Although the causal relationship between COPD and insomnia remains unclear, several factors may contribute to poor sleep quality.

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Therapies for Insomnia in Patients with COPD

- Shortness of breath may be exacerbated in the supine position, causing delayed sleep onset and arousals.
- Cough and excess mucus production also may worsen when people are supine and may contribute to delayed sleep onset.
- Nocturnal oxygen desaturation and hypercapnia may result from sleep-related hypoventilation and ventilation/perfusion mismatch in the supine position.
- Increased respiratory efforts associated with hypoxemia and hypercapnia may produce nighttime arousals.
- Drugs used to treat COPD, particularly systemic corticosteroids and beta-agonists, may further disrupt sleep.

Whatever the mechanism behind sleep disturbances in COPD, poor sleep may be self-perpetuating; sleep deprivation may decrease the ventilatory response to hypercapnia, further exacerbating desaturation and sleep disruption. Even a single night’s loss of sleep can result in notable, although not clinically relevant, changes in pulmonary function in COPD patients, but a night’s loss of sleep can result in notable, although not clinically relevant, changes in pulmonary function in COPD patients, but the effect of sleep disruption over multiple nights remains unknown. On the basis of this finding and with data showing that the effect of sleep disruption over multiple nights remains unexplained, changes in pulmonary function in COPD patients, but may be higher than direct costs, based in part on studies of which led to hospitalization.

Sleep disturbances have been independently associated with mortality in some populations, such as the elderly and men 45 to 65 years of age. Reduced quality of life, increased use of health care resources, and sleep disorders also have been identified as risk factors for falls in older patients. Falls were the leading cause of injury-related death among older adults in 2004, responsible for 14,900 deaths; they were also the most common cause of nonfatal injuries and trauma-related hospital admissions in this age group, resulting in 1.8 million ED visits (25% of which led to hospitalization).

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In general, individuals with sleep disorders have more medical and psychiatric illnesses, including depression and alcohol abuse, reduced quality of life, and increased use of health care resources. Sleep disorders also have been identified as risk factors for falls in older patients. Falls were the leading cause of injury-related death among older adults in 2004, responsible for 14,900 deaths; they were also the most common cause of nonfatal injuries and trauma-related hospital admissions in this age group, resulting in 1.8 million ED visits (25% of which led to hospitalization).

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In 1995, direct costs of insomnia were conservatively estimated at $13.9 billion. This figure included $2 billion for prescription and nonprescription agents used to treat insomnia. More recently, using an insurance database with more than 200,000 members, Ozminkowski et al. estimated that direct costs over a period of six months were $924 higher for adults 18 to 64 years of age with untreated insomnia compared with those without insomnia ($4,755 vs. $3,831, respectively; P < 0.01). Absenteeism costs were $405 higher for working members with insomnia compared with those without insomnia ($3,042 vs. $2,637, respectively; P < 0.0001). For members 65 years of age or older with untreated insomnia, six-month direct costs were $1,142 higher than for those who did not have sleeping difficulty ($3,790 vs. $4,648, respectively; P < 0.01).

The indirect costs of insomnia are more difficult to calculate but may be higher than direct costs, based in part on studies in other disease states. Indirect costs resulting from lost productivity and insomnia-related accidents, alcohol abuse, and depression may be as high as $77 billion to $92 billion per year.

TREATMENT

Because COPD patients are typically concerned primarily with their respiratory symptoms during physician visits, they might not describe sleep difficulties unless they are specifically asked. Management guidelines from the American Thoracic Society recommend that all COPD patients be questioned about sleep quality. However, optimal management of the COPD patient with insomnia requires treatment for both conditions to improve overall outcomes and to decrease health care use and costs.

General Management

The general approach to management of insomnia in patients with COPD is described in Table 1. Nonpharmacological strategies seek to modify behavioral and cognitive factors that may exacerbate sleep disturbances. Cognitive-behavioral therapy (CBT) addresses both types of factors and combines elements of psychotherapy with behavioral strategies, such as education about sleep hygiene. Although CBT can be effective and may provide long-term benefits, it is a time-intensive process. Thus, greater benefit may be derived when CBT is combined with pharmacological therapy, which may result in faster improvements in sleep.

Pharmacological Management

There are many approaches to the pharmacological management of insomnia, including prescription and nonprescription drugs and self-medication with alcohol. Alcohol may actually exacerbate insomnia, because it often results in poorer quality of sleep and frequent awakenings. Nonprescription medications include antihistamines (e.g., diphenhydramine) and herbal supplements (e.g., melatonin, valerian). However, few systematic data are available to support use of these products for the treatment of insomnia and antihistamines.

Table 1  General Approach to the Management of Insomnia in Patients with Chronic Obstructive Pulmonary Disease (COPD)

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Optimize the medical management of COPD to ensure that poor symptom control is not contributing to sleep disturbance.</td>
</tr>
<tr>
<td>2.</td>
<td>Assess use of all nonprescription and prescription drugs, limiting those that might exacerbate insomnia.</td>
</tr>
<tr>
<td>3.</td>
<td>Improve sleep hygiene:</td>
</tr>
<tr>
<td>3.1</td>
<td>Use the bed only for sleeping or sexual activity.</td>
</tr>
<tr>
<td>3.2</td>
<td>Insulate the bedroom environment against light and sound.</td>
</tr>
<tr>
<td>3.3</td>
<td>Keep the bedroom temperature cool.</td>
</tr>
<tr>
<td>3.4</td>
<td>Avoid excessive liquid intake, caffeine-containing beverages, and alcohol in the evening.</td>
</tr>
<tr>
<td>3.5</td>
<td>Avoid daytime naps.</td>
</tr>
<tr>
<td>3.6</td>
<td>Establish and maintain a bedtime routine before retiring.</td>
</tr>
<tr>
<td>4.</td>
<td>Consider pharmacological therapy in combination with nonpharmacological management.</td>
</tr>
</tbody>
</table>

Data based on text from George CFP, Bayliff CD. Drugs 2003; 63:379–387.
show reduced efficacy over time.\textsuperscript{27,30,31}

Although not approved by the FDA for the treatment of insomnia, sedating antidepressants (e.g., trazodone, amitriptyline) also have been used; however, data are limited regarding their efficacy in patients without comorbid depression.\textsuperscript{27,30,31} There is also a concern about tolerability with many of these agents,\textsuperscript{27,29–31} particularly those with anticholinergic effects, such as antihistamines and tricyclic antidepressants (TCAs). These agents should not be used as hypnotic drugs in adults 65 years of age or older because of their potential to cause delirium.\textsuperscript{27,31,32}

Ten prescription agents have been approved for the treatment of insomnia: nine benzodiazepine receptor agonists (BzRAs) and ramelteon (Rozerem, a melatonin receptor agonist) (Table 2).\textsuperscript{27,31,33}

**Benzodiazepine Receptor Agonists, Non-benzodiazepines**

The BzRAs include older benzodiazepine agents, such as flurazepam (Dalmane, Valeant), temazepam (Restoril, Mallinckrodt), and triazolam (Halcion, Pfizer) and newer non-benzodiazepine agents, such as zolpidem (Ambien, Sanofi-Aventis), zaleplon (Sonata, King), and eszopiclone (Lunesta, Sepracor). Clinical trials support the efficacy of these agents for the short-term treatment of insomnia in a general population.\textsuperscript{29} Except for eszopiclone and extended-release zolpidem, the labeling of the BzRAs restricts their use to short-term management of insomnia.\textsuperscript{31} The BzRAs are sedative–hypnotics that exert their effects by binding to sites on the gamma-aminobutyric acid-A (GABA\textsubscript{A}) receptor complexes in the brain.\textsuperscript{27,30,31} In addition to the sedative–hypnotic effects, the interaction of BzRAs with GABA\textsubscript{A} receptors may lead to numerous adverse effects, including residual daytime sedation, cognitive and psychomotor impairment (which may increase the risk of falls), and anterograde amnesia.\textsuperscript{27} Owing to their potential for abuse, all benzodiazepine and non-benzodiazepine BzRAs are designated as controlled substances by the Drug Enforcement Administration (DEA).\textsuperscript{27}

By virtue of their interaction with GABA\textsubscript{A} receptors, the BzRAs also have respiratory effects: they decrease the central respiratory drive and increase upper airway resistance by altering the activity of nerves that innervate upper airway muscles.\textsuperscript{10,11} Among other effects, this may result in increased oxygen desaturation, depression of the carbon dioxide ventilatory response, an increased number and duration of apneic episodes, decreased respiratory muscle strength, and a prolonged time to arousal following airway occlusion.\textsuperscript{11}

Adverse respiratory effects have been observed in both healthy subjects and patients with COPD,\textsuperscript{11} but patients with more advanced pulmonary disease or hypercapnia appear to be at greater risk.\textsuperscript{10} Respiratory depression also may be greater with cumulative doses.\textsuperscript{10} There is a higher prevalence of insomnia in the elderly; as such, the Beers criteria recommend against the use of long-acting BzRAs because of the potential for increased sedation, which can increase the risk of falls and fractures in this population.\textsuperscript{32} Furthermore, the Beers criteria suggest that short-term or intermediate-term BzRAs are preferred, if necessary, but smaller doses may be used for safety reasons.\textsuperscript{32}

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**Table 2 FDA-Approved Prescription Drugs for the Treatment of Insomnia**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset (Minutes)</th>
<th>Half-Life (Hours)*</th>
<th>Duration of Action</th>
<th>Dose Range (mg)</th>
<th>Insomnia Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepine receptor agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estazolam (Prosom)</td>
<td>60</td>
<td>10–24</td>
<td>Intermediate</td>
<td>0.5–2</td>
<td>Sleep maintenance</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>15–30</td>
<td>47–100</td>
<td>Long</td>
<td>15–30</td>
<td>Sleep maintenance</td>
</tr>
<tr>
<td>Quazepam (Doral)</td>
<td>20–45</td>
<td>25–84</td>
<td>Long</td>
<td>7.5–15</td>
<td>Sleep maintenance</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>30–60</td>
<td>4–18</td>
<td>Intermediate</td>
<td>7.5–30</td>
<td>Sleep maintenance</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>15–30</td>
<td>2–4</td>
<td>Short</td>
<td>0.125–0.25</td>
<td>Sleep onset</td>
</tr>
<tr>
<td><strong>Non-benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>30</td>
<td>6</td>
<td>Intermediate</td>
<td>1–3</td>
<td>Sleep maintenance</td>
</tr>
<tr>
<td>Zaleplon (Sonata)</td>
<td>20</td>
<td>0.5–1</td>
<td>Ultra-short</td>
<td>5–10</td>
<td>Sleep onset or sleep maintenance†</td>
</tr>
<tr>
<td>Zolpidem extended-release (Ambien)</td>
<td>30</td>
<td>1.4–4.5</td>
<td>Short</td>
<td>5–10</td>
<td>Sleep onset or sleep maintenance‡</td>
</tr>
<tr>
<td><strong>Melatonin receptor agonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramelteon (Rozerem)</td>
<td>45</td>
<td>1–2.6</td>
<td>Short</td>
<td>8</td>
<td>Sleep onset</td>
</tr>
</tbody>
</table>

* Includes active metabolites.
† For sleep maintenance; administered upon waking during the night.
‡ For sleep maintenance; extended-release formulation is recommended.

Data from Morin AK, et al. *Pharmacotherapy* 2007;27:89–110;\textsuperscript{27} Passarella S, Duong MT. *Am J Health Syst Pharm* 2008;65:927–934;\textsuperscript{31} and Rozerem (ramelteon), prescribing information.\textsuperscript{33}
Therapies for Insomnia in Patients with COPD

In general, however, data regarding the efficacy and safety of BzRAs and non-benzodiazepines in treating comorbid insomnia and COPD are limited. Most insomnia studies have been conducted in patients with mild-to-moderate COPD disease, and none of the studies have evaluated patients during COPD exacerbations. The newer non-benzodiazepine agents are thought to be safer than the older benzodiazepines, but there have been reports of respiratory effects with these agents.

Although non-benzodiazepines do have better overall safety profiles, they still carry similar safety risks. In a meta-analysis of sedative-hypnotic use in the elderly, Glass et al. found no significant differences in these classes in terms of cognitive and psychomotor adverse events.

Thus, the safety profile of the BzRs may present difficulties for certain patient populations, such as older adults and those with COPD or other pulmonary comorbidities. If BzRAs are used in older adults, dose reductions are often necessary to minimize the risk of falls and other adverse events. American Thoracic Society guidelines also recommend avoiding benzodiazepines in patients with COPD as a result of the potential negative effects on ventilation.

Although non-benzodiazepines are more selective for the alpha1-subunit of the GABA_A receptor and thus may have a lower frequency of adverse events than BzRAs, they are not typically recommended for routine use in patients with severe COPD or awake hypercapnia.

Ramelteon, a Melatonin Receptor Agonist

Among the drugs approved for the treatment of insomnia, ramelteon has a unique mechanism of action. This selective melatonin receptor agonist has a high affinity for the MT1 and MT2 receptors. When acted on by endogenous melatonin, these receptors contribute to the regulation of the body’s normal 24-hour sleep-wake cycle. The activity of ramelteon at the MT1 and MT2 receptors is thought to confer its sleep-promoting attributes.

Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset. Ramelteon has demonstrated efficacy for the treatment of chronic primary insomnia in several clinical trials. Although it is effective in decreasing latency to persistent sleep (LPS), its efficacy in improving other sleep parameters, as measured by polysomnography, has been mixed.

For example, in a randomized, double-blind trial that enrolled 405 otherwise healthy adults, 18 to 64 years of age, 8-mg and 16-mg doses were given nightly for five weeks. Compared with placebo, both doses of ramelteon significantly decreased LPS, as determined by polysomnography.

- at week 1 ($P < 0.001$ for both doses)
- at week 3 ($P = 0.001$ and $P < 0.001$ for 8 mg and 16 mg, respectively)
- at week 5 ($P = 0.007$ and $P = 0.002$, respectively).

For other sleep parameters, including total sleep time, sleep efficiency, and wake time after sleep onset (WASO), the results showed statistically significant differences for both doses compared with placebo at week 1 only.

Another randomized, double-blind study assessed the efficacy of ramelteon for chronic primary insomnia in 829 adults 65 years of age and older. Patients received nightly doses of ramelteon 4 mg, ramelteon 8 mg, or placebo for five weeks. Patient-reported data were collected in sleep diaries. Compared with placebo, both ramelteon doses reduced subjective sleep latency at weeks 1, 3, and 5 (except for the 4-mg dose at week 3) (see Figure 1). Furthermore, statistically significant increases in total sleep time were observed with ramelteon 4 mg at week 1 (324.6 vs. 313.9 minutes; $P = 0.004$) and week 3 (336.0 vs. 324.3 minutes; $P = 0.007$), but not at week 5.

There were no statistically significant differences between the 8-mg dose and placebo during the study. However, the number of awakenings, the ease of falling back asleep upon awakening, and sleep quality yielded no statistically significant differences with ramelteon at both doses, compared with placebo throughout the study.

Ramelteon was well tolerated in these trials, which included two-day and 35-day treatment courses in both younger and older age groups. Daily ramelteon doses ranged from 4 to 32 mg, and there were no differences between placebo and ramelteon on next-day performance or alertness measures.

In the studies evaluating five-week courses of ramelteon, there was no evidence of rebound insomnia or withdrawal during the run-out periods following drug discontinuation.

Furthermore, in a group of adults with a history of sedative abuse, ramelteon showed no significant effect on any subjective measurements of stimulant or sedative effects (including those related to abuse potential) or on observer-rated measurements of motor and cognitive performance, even at doses 20 times greater than the FDA-approved dose.

Ramelteon has been specifically demonstrated to be safe in two clinical trials of patients with COPD. In a randomized, double-blind, crossover study, Kryger et al. assessed the use of ramelteon in 26 patients with mild-to-moderate COPD. Subjects were not required to have a diagnosis of insomnia.

![Figure 1 Patient-reported mean sleep latency with ramelteon versus placebo in patients 65 years of age and older. (Reprinted from Roth T, et al. Sleep Med 2006;7:312–318. © 2006, with permission from Elsevier.38)](image-url)
They received either ramelteon 16 mg or placebo, followed by a 5-day to 12-day washout period. Assessments included overnight monitoring of arterial oxygen saturation (SaO2), apnea–hypopnea index (the number of apneic and hypopneic events per hour), and sleep parameters. There were no significant differences between treatment groups for any of the assessed respiratory parameters (Table 3).41,42 There were also no differences between the groups when SaO2 was compared for each hour of the night (Figure 2). Based on polysomnography, the total sleep time, sleep efficiency, and the number of awakenings were significantly improved with ramelteon (Table 3).41,42 There was also a trend toward a decreased WASO with ramelteon.

In light of these findings, Kryger et al. conducted a second study in 25 patients with moderate-to-severe COPD.42 The study design was similar to the previous trial in mild-to-moderate COPD, but patients received an 8-mg dose of ramelteon. Again, the patients were not required to have a diagnosis of insomnia. As with the patients with milder COPD, there were no significant differences between treatment groups for the assessed respiratory parameters (see Table 3).41,42 There also were no statistically significant differences when SaO2 was compared for each hour of the night, other than for the eighth hour (92.7% for ramelteon vs. 93.5% for placebo; \( P = 0.049 \)).

A subgroup analysis showed minimal treatment effect on SaO2 for the entire night when patients with moderate and severe COPD were analyzed separately. The sleep parameter data listed in Table 3 includes data for all 26 patients with mild-to-moderate COPD and all 25 patients with severe COPD.41,42 Total sleep time and sleep efficiency were significantly improved with ramelteon (see Table 3),41,42 with a trend toward improvement in LPS.

Although both Kryger studies had limitations such as the lack of an insomnia diagnosis as a requirement for inclusion in the study, these trials are considered important in the treatment of this population. Both studies were designed to evaluate safety by looking at respiration during sleep (and not the

Table 3 Effects of Ramelteon (Rozerem) on Mean Nighttime Respiratory and Polysomnographic Sleep Parameters in Patients with Chronic Obstructive Pulmonary Disease (COPD)*

<table>
<thead>
<tr>
<th>Respiratory parameter</th>
<th>Mild-to-Moderate COPD41</th>
<th>Severe COPD42</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo ((n = 26))</td>
<td>Ramelteon ((n = 26))</td>
</tr>
<tr>
<td>SaO2 entire night (%)</td>
<td>92.9</td>
<td>92.9†</td>
</tr>
<tr>
<td>% of night SaO2 &lt; 90%</td>
<td>12.0</td>
<td>13.4†</td>
</tr>
<tr>
<td>Apnea–hypopnea index</td>
<td>8.3</td>
<td>9.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep parameter†‡</th>
<th>Mild-to-Moderate COPD41</th>
<th>Severe COPD42</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (minutes)</td>
<td>353.6</td>
<td>380.6</td>
</tr>
<tr>
<td>LPS (minutes)</td>
<td>33.6</td>
<td>31.5</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>73.7</td>
<td>79.3</td>
</tr>
<tr>
<td>WASO (minutes)</td>
<td>97.1</td>
<td>76.4</td>
</tr>
<tr>
<td>NAW</td>
<td>9.5</td>
<td>11.1</td>
</tr>
</tbody>
</table>

LPS = latency to persistent sleep; NA = not available; NAW = number of awakenings; SaO2 = arterial oxygen saturation; TST = total sleep time; WASO = wake time after sleep onset.

* Patients were not required to have a diagnosis of insomnia.
† n = 25.
‡ Denotes data for entire study populations for both studies.

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effect in subjects reporting only insomnia); thus, patients with COPD with or without insomnia were enrolled. Because studies relating to the effects of insomnia agents in patients with COPD are limited, future research is needed to determine the impact of ramelteon and other insomnia agents on various sleep parameters in this population.

Ramelteon was well tolerated in patients with mild-to-moderate COPD and was not detrimental to those with severe COPD. The drug had little to no effect on measures of respiration, even though the dose used in the study of mild-to-moderate COPD was twice the FDA-approved dose. In the most recent study by Kryger et al., ramelteon did not worsen apnea in patients with mild-to-moderate sleep apnea. The apparent lack of effect of ramelteon on respiratory measures may be a consequence of its selective action on MT1/MT2 receptors, in contrast to the more generalized GABA-mediated central nervous system (CNS) depression seen with the BzRAs. In fact, the prescribing information for all agents in the non-benzodiazepine class suggests that they should be used with caution in individuals with compromised respiratory function.

DISCUSSION

There have been few, if any, direct head-to-head studies comparing the efficacy and safety of these drug classes in the treatment of comorbid insomnia and COPD. As such, further research is needed to determine the benefits and risks of these drug classes in this particular population. With the growing movement toward comparative effectiveness, including the recent $1.1 billion investment by the government, cost-effectiveness studies encompassing efficacy and safety, as well as the avoidance of potential adverse events and subsequent health care utilization, are essential pieces of the puzzle to determine which agents might provide the greatest clinical and economic benefit for all stakeholders—patients, providers, and payers.

For a variety of reasons, access to ramelteon is often restricted on many managed care formularies. As mentioned previously, numerous pharmacological options are available for sleep disorders—both nonprescription and prescription drugs—including those that are used off-label for insomnia. Many of these drugs are available in less expensive, generic formulations.

There has also been a perceived lack of efficacy for ramelteon compared with long-term BzRA use, in treatment-experienced patients. Thus, ramelteon has had an undefined value proposition for managed care. There is a need to identify those patients who would benefit most from treatment with ramelteon, such as treatment-naive patients or those who are significantly at risk from the adverse effects associated with the older sedative–hypnotic agents. Unlike the BzRAs, ramelteon shows no significant sedative adverse effects or potential for abuse.

In contrast, the Beers criteria identify the benzodiazepines, antihistamines, and amitriptyline as medications that carry a high risk of severe sequelae, such as falls, delirium, confusion, and toxic anticholinergic effects, in older adults. Also, unlike the BzRAs, ramelteon has not been shown to cause significant respiratory depression, even in patients with apnea or COPD. Considering the burden of COPD on the health care system and the prevalence of comorbid insomnia in that population, it may be valuable to have a formulary treatment option for insomnia that minimizes the risk of exacerbating the underlying pulmonary disease.

CONCLUSION

COPD is a highly prevalent medical condition in the U.S., and comorbid sleep disorders are common. Insomnia may increase the risk of falls and mortality, and it has an adverse effect on quality of life and health care utilization and costs. Among patients with COPD, sleep loss can have a negative impact on quality of life and pulmonary function. Treatment guidelines for COPD recommend that all patients be questioned specifically about sleep quality, because they might not otherwise volunteer this information.

Many options are available for the pharmacological management of insomnia, but most of these medications have limitations that may make them unattractive for use in patients with COPD. In particular, the BzRAs, which can cause GABA-mediated CNS depression, are associated with risks of cognitive and motor impairment and respiratory depression, particularly among older adults and those with underlying respiratory disease. Although non-benzodiazepines have better overall safety profiles, these drugs should be used with caution in individuals with compromised respiratory function.

Unlike traditional sedative–hypnotics, ramelteon has not been associated with these adverse effects, even when it is used at high doses or in patients with COPD or sleep apnea. However, because of the small sample sizes in these trials, additional study is warranted in high-risk COPD patients. Ramelteon appears to promote sleep onset without a significant sedative effect, leading some to describe it as a chronohypnotic agent because of its mechanism of regulating the body’s circadian rhythm. However, further research is needed to examine its sleep-promoting ability in patients with COPD and insomnia, especially its effect on other sleep parameters, including total sleep time, WASO, and sleep efficiency.

Access to ramelteon is limited on many managed care formularies because of the agent’s indeterminate value proposition. Given the prevalence and impact of both COPD and insomnia, it appears prudent to provide formulary access to ramelteon for select patients with decreased respiratory function or who may be at risk for sedative adverse effects associated with traditional insomnia agents. As further efficacy, safety, and cost-effectiveness data in patients with COPD and comorbid insomnia become available, the value of ramelteon as a treatment option may become clearer for this population.

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