



Could Melatonin Be an Alternative to Benzodiazepine for Chronic Obstructive Pulmonary Disease With Insomnia?

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Chronic obstructive pulmonary disease (COPD) is common, with a 10% global prevalence and a significant health problem, and is one of the main causes of morbidity. Patients with COPD experience various types of sleep problems with insomnia as the most common sleep disorder. The presence of sleep disorders further deteriorates their quality of life. Benzodiazepines (BZDs) are commonly prescribed drugs for insomnia. Several meta-analyses have shown that BZDs effectively reduce insomnia; however, severe side effects including rebound insomnia, next-day hangover, anterograde amnesia, and cognitive impairment occur. Since COPD patients often complain of symptoms such as shortness of breath, safe treatment for sleep disorders is needed. Melatonin supplements have a safe profile and are well-tolerated. Therefore, melatonin can be safely prescribed to treat insomnia in patients with COPD. In addition, due to the anti-inflammatory activity of melatonin, it can be an alternative to BZDs for improving insomnia symptoms without exacerbating respiratory symptoms. It would be helpful to more actively screen and detect sleep disorders in adults with COPD, and to provide safe melatonin treatment for improving their quality of life.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease characterized by chronic respiratory symptoms, structural pulmonary abnormalities, and airflow limitation [1]. COPD is highly common and is the third leading cause of death worldwide [2]. Sleep disturbance is one of the most common complaints in patients with COPD, and the presence of sleep disorders further deteriorates their quality of life [3]. Symptom exacerbations are associated with poor sleep quality in patients with COPD [4]. Patients with COPD experience sleep fragmentation with frequent arousals, reduced slow-wave, rapid eye movement (REM) sleep, and lower mean overnight oxygen saturation [5]. Insomnia is the most common sleep disorder in patients with COPD. Insomnia is defined as difficulty falling asleep and remaining asleep, as well as frequent awakenings during the night. In-

somnia is associated with comorbidities such as mental health disorders, cardiovascular diseases, and gastrointestinal diseases [6]. Although sleep disturbances are common and affect the quality of life of patients with COPD, sleep disorders are not widely detected or treated [7].

When patients with COPD develop insomnia, clinicians check whether respiratory symptoms worsen at night and adjust respiratory medications, and prescribe medications to improve sleep hygiene. In these cases, the most commonly prescribed medications are benzodiazepines (BDZs) [8]. A recent meta-analysis found that BZDs had a positive effect on sleep [9]. Despite improving sleep quality, BZDs have been associated with negative side effects such as falls, ataxia, and cognitive impairment in older adults [10]. Its use in patients with COPD was also associated with an increased risk of respiratory failure [11]. The long-term use of BZDs has become a public health concern, prompting sev-

eral campaigns to decrease their prescription and usage [12]. Due to these problems, interest in safer and effective treatments for COPD with insomnia has increased. Melatonin (*N*-acetyl-5-methoxytryptamine) is an endogenous hormone secreted by the pineal gland and plays a crucial role in the sleep-wake cycle of the body. Its production increases, facilitating good sleep and assistance in synchronizing circadian rhythms. Exogenous melatonin supplements have a safe profile and are well-tolerated. Therefore, it is now commonly used in the treatment of insomnia. The purpose of this review was to identify sleep problems in patients with COPD and explore the effectiveness and safety of melatonin in treating insomnia in these patients.

SLEEP DISTURBANCES IN COPD

Sleep disorders in patients with COPD are significantly high. In studies comparing sleep problems between patients with COPD and healthy individuals, approximately 16% of the healthy control groups complained of sleep problems, whereas 66%–78% of patients with COPD had sleep problems [13,14]. Patients with COPD have various sleep problems including insomnia, restless leg syndrome (RLS), parasomnia, and obstructive sleep apnea (OSA). Insomnia is the most common symptom reported by 23%–53% of patients with COPD [15,16]. The prevalence of RLS in the general population varies between 3% and 15%, whereas the prevalence of RLS in patients with COPD is reported to be 36.8% [14,17]. Although the pathophysiologic mechanism causing RLS in COPD is unknown, several factors may contribute to the cause. While RLS symptoms have psychogenic causes, they are also connected with hypoxemia and hypercapnia [18], and COPD is a significant respiratory disease that results in abnormal gas exchange [19]. The severity of dyspnea is linked with the severity of RLS symptoms [20]. Moreover, poor lung function and low serum ferritin levels may be the pathophysiological factors underlying RLS in patients with COPD [21]. Age also plays a key role in the development of RLS, as the prevalence of RLS increases with age in the general population. In general, apparent COPD manifests clinically between the ages of 40–50 years, with a 5-fold increased risk in the elderly compared to those under the age of 40. This information may help to explain why COPD is strongly associated with the development of RLS, particularly in people over the age of 65 [22]. Smoking may also be associated with COPD and RLS. It has generally been considered to aggravate RLS symptoms [5].

The coexistence of COPD and OSA is referred to as “overlap syndrome.” Patients with overlap syndrome have a significantly higher risk of morbidity and mortality than those with COPD or OSA alone [23]. It has been reported that airway and systemic inflammation are also associated with COPD and OSA, as both can cause difficulty breathing during sleep. Approximately 10% to 15% of people with COPD have sleep apnea [24,25]. Patients with overlap syndrome have more serious adverse effects, like nocturnal hypoxia and systemic inflammation, than patients with

either COPD or OSA alone, and are more likely to have high cardiovascular complications and more frequent COPD exacerbations [26,27].

Some studies have reported a relatively high incidence of OSA in patients with advanced COPD [24,25]. On the other hand, a population study found no correlation between COPD and OSA in a general population of middle-aged men and women [28]. It is still unclear if each disease increases the odds of incidence of the other or if they coexist together simply because of their high prevalence. Patients with COPD are more likely to suffer from OSA if they have a high body mass index (BMI) and a smoking history [29]. COPD-related factors that protect against OSA include low BMI, lung hyperinflation, older age, and diminished REM sleep [30].

Recent studies have also reported an increase in narcolepsy symptoms in patients with COPD [31]. Generally, sleep quality and quantity are considerably lower in patients with COPD [32]. Patients with COPD who are inappropriately managed for insomnia may have a higher risk of developing adverse respiratory problems, including acute exacerbation of COPD [33]. Therefore, it is critical to properly diagnose and treat sleep difficulties in patients with COPD.

MENTAL HEALTH AND SLEEP IN COPD

Patients with COPD are more likely to suffer from comorbid conditions such as anxiety and depression. According to research, approximately 16.2% of people with COPD have anxiety and 15.9% have depression [34]. One study reported that as many as 85% of people with both COPD and depression experienced sleep problems [35]. Patients with depression have significantly higher COPD Assessment Test (CAT) scores [36]. Moreover, poor health status increases the risk of anxiety by approximately six times and depression by approximately 2.6 times even in those with mild COPD [37]. In addition, pain is linked with insomnia in patients with COPD as individuals with COPD are more likely to complain of pain [38]. When individuals with COPD do not get adequate sleep, sleep problems can exacerbate chronic pain [38].

Behavioral, social, and biological variables all contribute to depression and anxiety symptoms in patients with COPD. The association between depression and COPD is likely to be bidirectional, according to a recent meta-analysis and systematic review [39]. Confounding factors include past cigarette smoking and nicotine dependence, which appear to play a substantial role in the associations between anxiety disorders and COPD [40]. Moreover, nicotine dependence appears to explain a significant portion of the correlation between mood problems and COPD. Cigarette smoking raises the risk and severity of COPD, makes daily activities difficult and distressing, and elevates the risk of anxiety or depression in patients with COPD. In addition, patients with COPD are more susceptible to physical discomfort and social isolation, while depression and anxiety were associated with hopelessness, low self-esteem, and social isolation. Emerging research

suggests that chronic low-grade inflammation mediates the relationship between depressive symptoms and pulmonary function. Elevated inflammatory markers were found to be associated with both depression [41] and COPD [42]. In a recent study, the link between depressive symptoms and pulmonary obstruction was partially explained by elevated levels of the inflammatory biomarkers such as C-reactive protein and interleukin-6 [43].

In a study of more than 40,000 patients with concurrent diagnoses of COPD and posttraumatic stress disorder, 24.4% of patients were prescribed long-term BZDs [44]. Most patients had mental health problems, including generalized anxiety disorders [44]. Inadequate access to mental health services increased the likelihood of long-term prescriptions (odds ratio [OR], 0.54; 95% confidence interval [CI]: 0.37–0.80). Due to a lack of awareness or access to mental health uses, alternative or non-drug treatment options are limited. There is a need to increase awareness of mental health and sleep problems for people with COPD and enhance access to treatment.

SLEEP PHYSIOLOGY IN COPD

The etiology of COPD-related sleep disruption is complicated and complex. Poorly controlled COPD-related symptoms, such as poor cough and dyspnea, can cause sleep disturbances. Physiological changes, ventilatory disturbances, inflammation, and medications in COPD patients may also be affected [5]. Sleep is a vulnerable period. Patients with COPD are more likely to experience a decrease in gas exchange when they sleep because of a lack of “wakefulness drive to breathe.” Hypercapnic chemosensitivity is also diminished, resulting in a change in ventilation during sleep for patients with COPD [45]. Patients with COPD may have severe desaturation during REM sleep, which is connected to atonia in the respiratory muscles [46].

Circadian clock dysfunction may contribute to COPD pathogenesis via inflammatory responses and oxidative stress. Inflammatory reactions and oxidative stress are the most frequently encountered variables in COPD, contributing to autophagy imbalance and circadian rhythm abnormalities. Several studies have demonstrated that many clock genes regulate the degree of autophagy [47].

In COPD, coughing is often suppressed during sleep. Hypersecretion may occur, impairing nocturnal gas exchange. Intermittent hypoxia is a critical mechanism in OSA, which is common in patients with COPD. It causes sympathetic hyperactivity and systemic inflammation, which may exacerbate the disease in patients with COPD predisposed to chronic hypoxia. OSA is directly associated with disease progression and poor clinical outcomes in patients with COPD [48].

SEVERITY OF COPD AND SLEEP DISTURBANCES

Various studies have been conducted on the association between COPD symptom severity and sleep disturbance; however,

the results have been inconsistent. There are reports of no association between the severity of airway obstruction and insomnia [49,50]. Some studies have shown that people with mild symptoms experience more sleep problems [51,52]. Among patients with COPD who were smokers, those with preserved lung function had more sleep disturbances than those with impaired airway obstruction [51]. Furthermore, another study demonstrated that greater arousal during sleep is related to less severe obstruction [52]. On the other hand, there have also been reports of sleep problems in people with severe respiratory symptoms. In the severe case of forced expiratory volume (FEV1) <50% in patients with COPD, there were many sleep disturbances and RLS was significantly increased [17]. Several researchers reported that more severe COPD worsens sleep [5,53].

Ban et al. [7] found that CAT scores can predict insomnia. Considering the correlation between a patient's CAT score and insomnia, when the CAT score was 14 or higher, the specificity was 71.5%, and the sensitivity was 66.7%. Insomnia severity was associated with the overall CAT score, physical activity level, sleep items, and breathlessness. However, this was not related to coughing. In that study, there was no association between pulmonary function test results and insomnia. Only 14.8% of patients with insomnia received appropriate treatment [7]. Further research is needed regarding the relationship and influencing factors between COPD symptom severity and sleep problems.

EFFICACY OF BZD IN COPD WITH INSOMNIA

Recently, many drugs have been prescribed for insomnia, including benzodiazepine receptor agonists (BZRA), melatonin receptor agonists, and low-dose quetiapine [54]. Of these, BZDs are the most prescribed. By binding to the BZ1 and BZ2 subtypes of the BZD receptor, BZDs act as a sedative via the GABA_A complex. Also, BZDs have hypnotic, anxiolytic, and anticonvulsant effects through the BZ1 receptor [55]. Several meta-analyses have shown that BZDs effectively reduce insomnia, but severe side effects include next-day hangover, rebound insomnia, anterograde amnesia, and cognitive impairment [56].

In a recent meta-analysis of the effect of BZDs on insomnia in COPD patients, in which BZDs were compared to a placebo, BZDs significantly improved objective sleep quality. Total sleep time, sleep efficiency, and sleep latency were all included as outcome variables. Additionally, the number of arousals during sleep was decreased. However, BZD treatment did not affect respiration or subjective sleep quality [9].

Zolpidem, one of the non-BZD (Z type) drugs, is commonly used for treating insomnia. It has a high affinity and selectivity for the $\alpha 1$ -subunit of the GABA_A receptor complex. Zolpidem helps with sleep maintenance; however, it may cause headaches, drowsiness, dizziness, and nausea [57]. The use of BZRAs was found to be a significant risk factor for respiratory failure in patients with COPD. BZRAs increased the risk of respiratory failure (adjusted

odds ratio [AOR], 1.56; 95% CI, 1.14–2.13) [11]. Those who received two or more types of BZRAs or used a mix of BZD and non-BZD medication had a two-fold increase in the risk of respiratory failure [11].

RISK OF BZD USE IN COPD WITH INSOMNIA

Few studies have shown that BZDs are associated with a higher risk of a drug overdose, hypercapnic respiratory failure, acute COPD exacerbation, pneumonia, and death [10]. A recent retrospective cohort study discovered that the one-year cumulative incidence of bloodstream infections in patients taking BZDs was 2.3% [58]. Díez-Manglano et al. [59] reported that patients with COPD consumed more BZDs ($p=0.037$) than control patients and that BZD usage was independently related to an increased risk of hip fracture.

The prevalence of COPD increases with age. BZD use is also age-related [56]. People taking BZDs were more likely to have somnolence as well as COPD exacerbations and respiratory infections. A longitudinal analysis of data over 20 years conducted by Wouters et al. [60] found that higher long-term cumulative exposure to medications was associated with poorer cognitive and physical functioning. Even if BZDs are prescribed for insomnia, they are likely to increase the risk of accidental abuse or suicide [61].

Concomitant use of opioids and BZDs also exacerbates respiratory symptoms in COPD [62]. Additionally, concurrent use of opioids was related to a nearly 10-fold increase in significant risk of death when compared to opioid use alone [62]. In a study using a national database in Taiwan, the BZD receiving group showed significantly increased admission for acute exacerbation of COPD compared with that of the non-user group, with a relative risk (RR) of 2.52 (95% CI, 1.52–4.18) [10].

The use of BZDs was also associated with the maintenance of intubation. Reintubation was significantly associated with the administration of sedatives/analgesics prior to extubation (OR, 8.6; 95% CI, 1.23–60.8) [63]. Additionally, it was found that BZD use is related to delirium in the elderly. Rothberg et al. [64] examined the association between sedative medication and delirium in a large cohort of hospitalized elderly adults and found that short-acting BZDs (AOR, 1.18; 95% CI, 1.03–1.34) were associated with a greater risk of subsequent delirium.

In another study, new BZD users had a significantly increased incidence of emergency room visits for COPD or pneumonia (RR, 1.92; 95% CI, 1.69–2.18) and outpatient respiratory exacerbations (RR, 1.45; 95% CI, 1.36–1.54) compared to non-users [65]. BZDs were associated with increased mortality (RR, 1.21; 95% CI, 1.05–1.39) with a dose-response trend [66]. Caution should be considered when concurrently using opioids and BZDs, especially in patients with COPD.

Research about BZD use and associated risk factors showed that BZD users were more likely to suffer from depressive disorders (OR, 2.7), substance abuse (OR, 2.2), tobacco use (OR, 1.7),

and alcohol abuse (OR, 1.5). In addition, BZD prescriptions were more frequent in patients with physical diseases, such as COPD (OR, 1.6), sleep apnea (OR, 1.5), and asthma (OR, 1.5) [12]. The risk increases further when BZD is used in the elderly [56]. These risks should be considered when prescribing BZDs.

PATTERNS OF BZD USE IN COPD PATIENTS

Patients, healthcare providers, and regional variables influenced the prescribing patterns of long-acting BZDs for the elderly. In a nationwide study, prescriptions for long-acting BZDs accounted for 44.7% of prescriptions. The most frequently prescribed BZD was diazepam (39.7%). Moreover, 3.5% of patients prescribed long-acting BZDs had COPD. The use of long-acting BZD varied significantly between medical institutions. Long-acting BZDs were most commonly administered in primary-care settings and rural areas [67].

Especially, recipients of high-dose BZDs were even more likely to have specific medical diagnoses including alcohol abuse (OR, 3.2; 95% CI, 2.2–4.5), substance abuse (OR, 7.5; 95% CI, 5.5–10.1), tobacco use (OR, 2.7; 95% CI, 2.1–3.5), and COPD (OR, 1.5; 95% CI, 1.2–1.9) [12]. BZD users had more primary care visits, specialist outpatient visits, emergency visits, and hospitalizations. Thus, BZD prescription was associated with increased healthcare utilization [12]. In a population-based study by Vozoris et al. [68], 31.7% of patients with COPD were prescribed a new BZD. Those with more severe COPD were more likely to receive new BZD prescriptions (AOR, 1.43; 95% CI, 1.38–1.48). COPD patients who were new BZD users had a relatively high frequency of receiving long-acting BZDs (14.6%), early refills (11.6%), dispensations for greater than 30 days (32.6%), and BZD prescriptions during COPD exacerbations (9.0%) [68]. BZD prescription is related to various factors; therefore, a proper understanding of risk factors is required for adequate intervention.

MECHANISM OF BZDS ON RESPIRATORY FUNCTION

BZDs affect respiratory function by several mechanisms. By binding to BZD receptors, particularly the BZ2 receptor, BZDs may reduce the central ventilatory drive by activating the GABA system in motor neurons and the limbic system [69]. BZDs may raise the arousal threshold, resulting in delayed airway opening and aggravation of hypoxia and hypercapnia [70]. Furthermore, BZDs may decrease muscular tone in upper airway dilator muscles that are already functionally damaged [71,72]. Additionally, BZD use in OSA patients may result in a decrease in the rate of the cyclic alternating pattern seen during non-REM (NREM) sleep, resulting in decreased resilience to adverse respiratory episodes [73]. In electroencephalography, the cyclic alternating pattern is a measure of sleep instability that represents the brain's attempt to maintain the sleep structure [74].

MELATONIN AND SLEEP PHYSIOLOGY

Endogenous melatonin levels begin to rise roughly 2 hours before the onset of sleep and reach a peak approximately 5 hours later [75]. Reduced melatonin production may contribute to insomnia. Due to melatonin levels declining with age, older persons are more likely to experience insufficient melatonin levels [76]. The ability to sleep and sleep architecture changes with age, which leads to a significant reduction in slow-wave NREM sleep [77]. Lower melatonin levels have been linked to symptom exacerbation and low quality of life in patients with COPD [78].

Melatonin is a ubiquitous chemical found in plants, fungi, and animals and has functional activity in all of them. Melatonin has been synthesized as an internal sleep facilitator to treat sleep problems and improve sleep [79]. Additionally, melatonin is a biogenic amine that exhibits a wide range of biological functions, including anti-inflammatory, antioxidant, anti-aging, anticancer, antiviral, antidiabetic, and neuroprotective properties [80].

Melatonin's half-life is relatively short. As a result, immediate-release melatonin is rapidly metabolized and eliminated after 90 minutes. These characteristics effectively reduce sleep latency but have little effect on improving sleep quality or awakening at night. Therefore, sustained-release formulations of melatonin can compensate for these limitations that are currently mainly prescribed.

EFFICACY OF MELATONIN FOR INSOMNIA IN PATIENTS WITH COPD

The therapeutic effects of melatonin on insomnia have been confirmed in several studies. It was effective for insomnia in children with attention-deficit/hyperactivity disorder or autism spectrum disorder and improved sleep quality in older adults with Alzheimer's disease [81-83]. By imitating natural endogenous melatonin, exogenous melatonin can treat insomnia by attaching to the same receptors and activating the pathway. Supplementing with melatonin increases sleep efficiency, prolongs total sleep time, and shortens sleep onset latency [84]. The use of 3 mg of melatonin per night resulted in a reduction in REM sleep without atonia, as well as changes in symptoms of REM behavior disorder [85].

A recent meta-analysis of 23 studies on melatonin and sleep indicated that melatonin has a notable effect on the quality of sleep [86]. Several studies have shown that melatonin may promote BZD discontinuation. A retrospective study using a German database demonstrated that 31% of patients discontinued BZDs 3 months after beginning prolonged-release melatonin (2 mg) treatment [87]. Siegrist et al. [88] reported that the efficacy of melatonin in reducing BZD use was demonstrated when 65% of patients with insomnia receiving BZDs and melatonin (3 mg) were able to discontinue BZD use. Moreover, patients taking melatonin reduced BZD doses to 25%–66% of the initial doses [88]. Therefore, melatonin can help the discontinuation of BZDs in older individuals with insomnia.

Melatonin is effective in patients with COPD with insomnia [89]. In a randomized double-blind placebo-controlled study, Nunes et al. [90] investigated the efficacy of melatonin on sleep and respiratory function in patients with COPD. For 3 weeks, patients received melatonin or placebo in 3 mg doses, 1 hour before sleep. The melatonin treatment significantly improved sleep onset and sleep duration. Moreover, melatonin did not affect daytime drowsiness, exercise performance, and pulmonary function [90].

In a study of older patients with COPD, melatonin also improved sleep. The study randomly divided the patients with COPD into two groups. While COPD treatment continued, Group 1 received 3 mg of melatonin 30 minutes before sleep for 2 weeks, and Group 2 received no medication. After 12 months of follow-up, COPD exacerbation and hospitalization were significantly reduced in the melatonin-treated group. Additionally, along with improving sleep quality in patients with COPD during treatment, anxiety and depressive symptoms also improved [91].

Melatonin is also effective in reducing REM sleep behavior disorder (RBD) symptoms. Melatonin's mechanism of action against RBD may involve a combination of factors, including a direct effect on REM sleep atonia, modulation of GABAergic inhibition, stabilization of circadian clock variability and desynchronization, and enhancement of sleep efficiency [92-95]. By enhancing the activity of GABA on GABA_A receptors on anterior horn cells, melatonin may reduce behavioral symptoms of RBD. Melatonin may also decrease calmodulin, which modulates cytoskeletal structure and nicotinic acetylcholine receptor expression in skeletal muscle cells [96]. Melatonin was more effective than clonazepam at decreasing REM motor activities and restoring REM muscle atonia in a glycine/GABA_A receptor knock-out transgenic mouse model of RBD [97].

Several studies have investigated the effects of melatonin in patients in the intensive care unit (ICU). Patients in the ICU were administered melatonin 3 mg at around 10:00 PM, and sleep quality was measured using wrist actigraphy. Sleep duration and quality improved significantly in this group [98]. A randomized, double-blind, placebo-controlled trial showed that patients with severe COPD with poor sleep quality had efficacy from oral 3 mg melatonin treatment compared to the placebo. Melatonin significantly improved sleep quality, latency, duration, and efficacy. However, there were no significant differences in daytime sleepiness, lung function, or oxygenation [99]. Melatonin improves sleep quality in healthy adults exposed to simulated ICU light and noise [100].

Drugs that act on melatonin receptors are also effective against insomnia. Ramelteon (melatonin receptor agonist) effectively increases sleep efficiency and total sleep time and reduces sleep latency. Agomelatine is a powerful melatonin-receptor agonist with a relatively weak serotonin 5HT_{2C} receptor antagonism and has been approved as an antidepressant. A previous study investigated the utility of 8 mg ramelteon versus placebo in patients with COPD and insomnia and assessed polysomnography, respiratory function, and oxygen saturation. The ramelteon group had improved sleep efficiency and total sleep time, although there was

no significant difference in respiratory function [101].

The effective melatonin dosage for insomnia depends on individual characteristics. It is usually taken 15–60 minutes before bedtime, and the daily dose varies from 1–23 mg. Even at doses of 2–3 mg, it is effective for sleep.

EFFECT OF MELATONIN ON THE RESPIRATORY SYSTEM

Many studies have been conducted on the effects of melatonin on sleep in patients with COPD. Melatonin reduced lung oxidative stress in patients with COPD who received melatonin at 3 mg/day for 3 months. Melatonin treatment was found to improve the severity of oxidative stress and dyspnea in patients with COPD [102]. Moreover, melatonin has been linked to increased antioxidant levels in pulmonary cells [103].

In addition, melatonin suppressed acrolein-induced interleukin 8 production in human lung fibroblasts from patients with COPD. Melatonin can affect cell proliferation, growth, and survival in patients with COPD [104]. Preclinical studies in COPD have reported that melatonin influences classical aging-associated pathways to increase pulmonary sirtuin-1 [105]. Notably, melatonin inhibits excessive mucus secretion and attenuates neutrophil inflammation in cigarette smoke-induced COPD [106]. Furthermore, melatonin alleviates pulmonary hypertension due to chronic hypoxia, which is associated with COPD [107]. All these results indicate that melatonin treatment can improve the pathophysiology of COPD.

A recent study showed that melatonin reduced the sedative use and the duration of mechanical ventilation for patients with intracerebral hemorrhage in the ICU [108]. The results indicated that the mechanical ventilation time and cumulative doses of morphine were significantly lower in the group treated with melatonin [108]. Hyposecretion of melatonin during mechanical ventilation and disturbed diurnal rhythm has been observed in most patients treated in the ICU [109]. A previous study found that the level of 6-sulphatoxymelatonin (6-SOM, a metabolite of melatonin) in morning urine was 1.2 times lower in the group with COPD and gastroesophageal reflux disease (GERD) than in the isolated GERD group, and 1.9 times lower than the control group. Higher COPD severity was associated with a lower concentration of 6-SOM [110]. These results suggest there is a correlation between melatonin concentration and symptom severity in patients with COPD.

SAFETY OF MELATONIN

Compared with other sleep medications, melatonin is well tolerated and has a low risk of addiction [111]. Furthermore, continuous melatonin use was not associated with rebound insomnia [112]. There is no evidence of tolerance or dependence, nor is there any effect on mood and alertness the next day [113]. Although side effects such as headache, dizziness, nausea, and drows-

ness are possible, they are insignificant when used at low doses. Melatonin dosages of 20–100 mg/day in healthy volunteers have been found to be well-tolerated with no adverse effects on physiological or biochemical parameters [114].

Therefore, melatonin may be an appropriate first-line treatment for insomnia in patients with COPD. Ideally, hypnotics should have no undesirable side effects such as impairment of cognition, subsequent psychomotor retardation, or daytime hangover symptoms, nor should they have the potential for abuse. Melatonin satisfies several of these criteria [115].

CONCLUSION

Sleep problems are common with COPD and are related to quality of life. Although the early diagnosis of insomnia in patients with COPD is not easy, it is important to properly treat insomnia. However, caution is needed when selecting medication for insomnia due to the possibility of worsening respiratory symptoms. Melatonin is effective for the treatment of insomnia in patients with COPD. In addition, due to the anti-inflammatory activity of melatonin, it can be an alternative to BZDs for improving insomnia symptoms without exacerbating respiratory symptoms. According to our review, adults with COPD should be rigorously evaluated for sleep disorders. Melatonin has the significant advantages of a safe profile, is well-tolerated, and can be administered to patients for longer durations without the risk of abuse.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Author Contributions

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