Drugs 2003; 63 (4): 379-387
0012-6667/03/0004-0379/$33.00/0

Management of Insomnia in Patients With Chronic Obstructive Pulmonary Disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is a common medical disorder, which causes considerable morbidity and mortality. Given the chronic and symptomatic nature of the disease, the patient is often seen in the physician's office with complaints of dyspnea. However, more than 50% of COPD patients also have sleep complaints characterised by longer latency to falling asleep, more frequent arousals and awakenings, and/or generalised insomnia. Sleep disturbance tends to be more severe with advancing disease and substantially reduces the COPD patients' quality of life.

In approaching the COPD patient who complains of insomnia it is important to take a complete sleep history. Having characterised the degree and duration of the problem, medical management of the underlying COPD must first optimise oxygen saturation while minimising the effects of many of the medications used for COPD. While aerosol therapies may be systemically absorbed and contribute to sleep disruption, anticholinergics, such as ipratropium bromide, are the least likely to do so and indeed have been shown to improve sleep quality in this population.

Many of the traditional sedatives and hypnotics have been used in the COPD population including benzodiazepines, imidazopyridines, pyrazolopyrimidines and, less commonly, antidepressants and phenothiazines. Clinical trials support the role of numerous agents in treating insomnia in this population but do not always provide reassurance that these therapies can be used safely, particularly in the patient with severe COPD with hypercarbia. Benzodiazepines are among the most commonly employed agents, but case reports and series continue to

describe adverse pulmonary events. Although the newer pyridine derivatives also have the potential to worsen pulmonary function, they appear less likely to do so. Data to date are limited with the tricyclic antidepressants and phenothiazines, although they appear to be very well tolerated from a respiratory point of view.

Since sleep disturbances are often long-standing and associated with maladaptive behaviours towards sleep, cognitive/behavioural approaches are often useful and are more effective in the long-term than are hypnotics. When prescription of a sedative is to be made, extra caution is required for those patients at increased risk of adverse respiratory effects, such as those with advanced disease and hypercarbia in whom pharmacological therapy is often best avoided. Selection of the various options will depend upon the degree of underlying disease and the patient's specific complaints of insomnia. Finally, it is important to remember that while most hypnotics work in an acute setting, the long-term management will require an integrated approach.

Chronic obstructive pulmonary disease (COPD) is a common and serious medical disorder which affects about 20% of North Americans and is the fourth leading cause of death in the US.[1] COPD is a disease state characterised by airflow obstruction due to chronic bronchitis or emphysema. The airflow obstruction is generally progressive, often accompanied by bronchial hyper-reactivity, and may be partially reversible.[2-5] As with most chronic diseases, quality of life can be impaired in a number of ways. While chronic pulmonary symptoms (e.g. cough, phlegm and shortness of breath) are the usual focus of most patient-initiated physician visits, patients with COPD frequently have difficulties with sleep. In the Tucson Epidemiologic Study[6] more than 50% of the patients with chronic bronchitis or emphysema complained of difficulties initiating and/or maintaining sleep, whereas 25% complained of excessive daytime sleepiness.[1,6] Indeed the quality of sleep has tremendous influence on the quality of waking life, and this is particularly important in patients with COPD.[7,8] Practitioners should be challenged to ask patients if they are experiencing any sleep abnormalities.[9] By so doing, and by understanding the abnormalities in sleep secondary to COPD and the various treatment options available, the practitioner can successfully reduce the burden of disease in patients with COPD.

1. Normal Sleep

Although sleep may be defined in behavioural terms – a state where perception of, and response to, the external environment in reduced or absent – sleep is also defined in terms of the electroencephalogram (EEG) and is divided into two states. Rapid eye movement (REM) sleep is characterised by an active EEG, which is desynchronised across hemispheres, bursts of rapid eye movements and loss of postural muscle tone. Apart from movements of the eyes and diaphragm (and other muscles of respiration), REM is a state of paralysis. It is during this time that most dream mentation occurs. Non-REM (NREM) sleep lacks rapid eye movements and is divided into four stages based on EEG. These four stages roughly parallel the depth of sleep with arousal threshold lowest in Stage 1 and highest in Stage 4 NREM sleep. The EEG is synchronous and characteristic waveforms (spindles, K-Complexes, high voltage slow waves) are found during NREM sleep. Breathing during sleep is state specific and ventilatory responses to hypoxaemia and hypercapnia differ from REM to NREM sleep.[10] Such differences may be important when considering sedative medications with variable respiratory depressant effects.

Normally, sleep progresses in an orderly fashion throughout the night with REM sleep alternating with NREM sleep at about 90-minute intervals in adults. REM sleep episodes generally become

longer across the night, while slow wave sleep (Stages 3,4) become shorter or disappear altogether. The average length of the first NREM-REM sleep cycle is 70–100 minutes. The second and subsequent NREM-REM cycles are 90–120 minutes in duration.

Many factors can influence the expression and distribution of sleep. The strongest and most consistent of these factors is age, which is particularly important when considering the COPD population. Sleep is also influenced by homeostatic and circadian influences. The homeostatic control is very sensitive to prior sleep history. In other words, the less the previous sleep period, the greater propensity there is to have more and deeper sleep during a recovery night.[11]

The timing and type of sleep is dependent on time of day. Temperature also has an important influence on sleep. Extreme environmental temperature will disrupt sleep, especially REM sleep since ability to regulate internal body temperature is impaired during this stage of sleep. The duration and distribution of sleep may be affected by a host of drugs, including those for the treatment of sleep disorders and medical conditions such as COPD (*vide infra*). These will be discussed in the context of treatment of sleep and COPD.[11]

2. Sleep in Chronic Obstructive Pulmonary Disease (COPD) Patients

Sleep in patients with COPD is characterised by longer latency to sleep onset, more frequent arousals and awakenings, more frequent stage changes and poorer sleep efficiency than normal individuals.[12] The degree of sleep disturbance is variable with a rough correlation to the degree of the underlying lung disease.[12] Moreover, sleep disturbance found in patients with chronic airflow limitation is consistently associated with reduced quality of life.[7,8]

Poor sleep quality is common in this population for several reasons. Firstly, cough and excessive mucus production may delay sleep onset, particularly because these symptoms may be exaggerated in the supine position. Shortness of breath may also be exaggerated by position and COPD patients may have episodes of nocturnal dyspnea, which produce frequent awakenings. Increased work of breathing associated with chronic airflow limitation may also contribute to the pathogenesis of sleep disruption in these patients since increased ventilatory effort is a potent stimulus for arousal from sleep.[13] Once asleep, these patients are at risk for oxygen desaturation as a result of multiple mechanisms. Sleep-related hypoventilation secondary to reduced neural drive is the predominant reason,[14] but a reduction in functional residual capacity and increased ventilation-perfusion mismatch may also contribute to oxygen desaturation. Such changes are most obvious during REM sleep when postural muscle tone is absent.[12] In response to hypoxaemia and/or hypercapnia, ventilation and respiratory effort both increase. Although the arousal response to hypoxaemia is not always consistent, the increased effort of breathing may produce arousal.

The severity of the hypoxaemia during sleep can be predicted from the degree of depression of the waking ventilatory response to hypercapnia.[12] Supplemental oxygen therapy during sleep can offset significant hypoxaemia, yet sleep quality may not improve substantially.[15,16] This suggests that still other factors are involved in the sleep disturbance. However, improving oxygenation as a result of reducing airflow obstruction may result in improved sleep quality and/or duration.[17,18]

Although not specific to COPD patients, medications used in the management of COPD may also contribute to insomnia. It is well recognised in clinical practice that corticosteroids can produce insomnia[19] and that β-adrenoceptor agonists may produce sufficient adrenergic stimulation to interfere with initiating and maintaining sleep. This may apply in particular to cystic fibrosis patients who routinely take inhaled β-agonists just before going to bed.[20] As cystic fibrosis patients are much younger than typical COPD patients, but have a similar degree of airflow obstruction, this suggests that the effects of the chronic disease itself outweigh effects of age on sleep.

The use of theophylline (1,3-dimethlyxanthine) might be easily implicated in sleep disturbance in patients with COPD by virtue of its chemical similarity to caffeine (1,3,7-trimethylxanthine). However, most of the literature does not support a role for worsening sleep in patients receiving theophylline[21-24] and, given that lung function may improve, the potential interference with sleep may be offset by the potential benefit in lung function.[25]

Regardless of the mechanisms, poor sleep may be self-perpetuating since sleep deprivation may attenuate the ventilatory response to hypercapnia in patients with COPD[26] leading to further desaturation and sleep disruption. Thus, it is important to address the problem of sleep disorders in patients with COPD because it may substantially improve the quality of life in these patients.[4]

3. Pharmacotherapy for Sleep Disorders in COPD Patients

While acknowledging that sleep disorders are common in patients with COPD, correcting the problem with pharmacological therapy is challenging for several reasons. Firstly, insomnia in this patient population is often multifactorial in nature. In addition, observational studies continue to suggest that the use of certain hypnotics have been associated with ill health including risk of falls and fractures[27] and pneumonia.[28] Thirdly, the studies (discussed later in this section) evaluating the role of hypnotics in COPD patients are generally methodologically flawed by their short duration. Finally, the chronic and often severe lung disease seen in these patients necessitates extreme caution in management of insomnia. Keeping these issues in mind, it is essential that sedatives or hypnotics only be prescribed after a comprehensive assessment of the benefits and risk of treating or not treating a particular patient.

The use of hypnotics is common, particularly in the elderly. A recent Canadian survey of almost 4000 elderly patients (mean age 72 ± 7 years) indicated that, in the previous year, 53% had used hypnotics, with prescription products accounting for 83% of the hypnotics used.[29] Of these, benzodiazepines were most commonly used. Furthermore, use was regular, as 50% of respondents indicated that they use a hypnotic on a daily basis, and use was long-term, with a mean duration of therapy of 6 years (ranging from 2 weeks to 30 years).

Unfortunately many of the trials in patients with COPD have been performed primarily to allay concerns about toxicity. From an efficacy point of view, there are several methodological limitations. Often these trials are of short duration usually only a few nights or even limited to a single night despite the fact that much of the hypnotic use is chronic.

The most commonly employed agents have traditionally been benzodiazepines. More recently imidazopyridines and pyrazolopyrimidines have been used, and, less commonly antidepressant and phenothiazine therapy have been employed. As well, melatonin has been used, although the data is very limited and is not generalisable to the population as a whole.[30] The older hypnotics – chloral hydrate, glutethimide and methyprylon – are either no longer available or have fallen out of use for COPD patients. Over-the-counter sleep aids are available and still used, with diphenhydramine, a sedating antihistamine, being one of the more common agents, but again this agent has not been studied in patients with COPD.[31]

There have been a number of trials in COPD patients using benzodiazepines including lorazepam,[32] triazolam,[33-36] diazepam,[37] nitrazepam,[38] flurazepam,[39,40] flunitrazepam[33,35,38] and estazolam.[39] In addition, trials have used zolpidem[35,36,41] and zopiclone[42] in the COPD population, and there is one published report (in abstract form) of the use of zaleplon in this population.[43] Two trials have been published that describe the use of a phenothiazine[44] and an antidepressant[45] as a hypnotic in this population. The results of these studies are generally consistent, demonstrating shorter sleep latency, fewer awakenings and increased sleep duration.

However, the short duration of these trials limits the ability to identify adverse effects (especially in

patients taking benzodiazepines) since the toxicity may be greater with cumulative doses. In addition, specific risk factors for respiratory depression secondary to sedatives are evident from both clinical trials and case reports.[46,47] Two factors that appear to have a marked influence on adverse outcomes are more advanced disease and the presence of hypercarbia.[48-51] In the studies reviewed which looked at risk of respiratory depression, two of the studies[33,37] involved normal volunteers and four studied patients with mild to moderate disease as identified by forced expiratory volume in 1 second (FEV_1) and lack of CO_2 retention.[36,38-40] In those studies in which patients who had more advanced disease,[32,34,41] CO_2 retention was noted in only a minority of patients i.e. 30% in one study[34] or was of a relatively low order i.e. partial pressure of alveolar CO_2 ($PaCO_2$) 47 ± 5 mmHg in another study.[41]

Benzodiazepines are known to cause problems in some patients with obstructive lung disease. Respiratory depression from benzodiazepines is associated with a reduced tidal volume leading to hypercapnia, which may persist for several hours.[52] Midazolam, a short-acting benzodiazepine, has been shown to reduce ventilatory response and mouth occlusion pressure response to carbon dioxide.[48] Benzodiazepines preferentially alter activity of the cranial nerves that innervate upper airway muscles,[53] and selective inhibition of the hypoglossal and recurrent laryngeal nerves over the phrenic nerve can lead to airway obstruction and direct depression of motor nerves.[54]

In addition, it appears that patients with COPD are predisposed to the respiratory depressant effects of benzodiazepines. When compared with healthy controls the onset of respiratory depression was faster in COPD patients (2 vs 3.5 minutes for controls) and patients with COPD required twice as long to return to baseline level pulmonary function.[48] In another study, respiratory depression was more pronounced in patients taking midazolam than in those receiving thiopental preanaesthesia.[49] In practice, although a single dose may result in obtundation and decreased ventilation in a given patient, the effect may also be cumulative and so the patient who has tolerated a single dose may still be at risk of respiratory depression.[50,51] Indeed different additive mechanisms may be involved in this situation, with diminished respiratory drive leading to retention of secretions and further compromised pulmonary function.

While there are few direct comparative trials, it appears that, in terms of safety, the available data support that the imidazopyridines are safer in COPD patients than are the benzodiazepines, given the methodological limitations of the studies.[35,37] In a study in COPD patients, zopiclone therapy was associated with an increase in the number of apnoeic spells and the duration of these, albeit not in a statistically significant fashion.[42] On the basis of this, the authors suggested that zopiclone acts as a moderate respiratory depressant but without a deleterious effect on night-time oxygen delivery. That respiratory depression has been cited in case reports using zopiclone further emphasises the limitations and extent of current study in the area of COPD.[47]

Two of the studies reviewed detailed the efficacy and toxicity of other agents in the COPD population.[44,45] In a single dose study[44] propiomazine, a sedating phenothiazine derivative, administered to 12 patients with moderate COPD was found to enhance sleep efficiency and total sleep time without having any adverse respiratory effects. In another study,[45] 10 stable COPD patients received protriptyline 10–20mg for 2–4 months. While sleep efficiency and latency were not favourably affected, protriptyline, an antidepressant, improved baseline partial pressure of alveolar oxygen (PaO_2), reduced the nocturnal decline in arterial oxygen concentration (SaO_2) and improved the lowest SaO_2. While tolerated from a respiratory system aspect, tolerance in this long-term study was a problem with xerostomia and dysuria being reported frequently.[45]

Doxepin, a sedating antidepressant, has been found to be useful both in the short-term (day 1) and over a longer treatment period (28 days), with

minimal risk of rebound insomnia in patients with insomnia.[55] Unfortunately, the drug has not been studied in patients with COPD but, given the suggestion that antidepressant medications may be useful in managing dyspnea in patients with COPD, future trials are warranted.[55] A single case report details that tricyclic antidepressants may have a deleterious effect on ventilatory control.[56] This appears to be at odds with other data which describe the safety of these drugs in this setting[45] and the clinical relevance of this finding is unknown.

While some benefit of selective serotonin reuptake inhibitors (SSRI) in the management of dyspnoea in patients with COPD has been described,[57] the current literature on SSRIs would suggest that these agents may disrupt sleep.[58] Before SSRIs can be recommended, further trials assessing both the impact on anxiety and sleep are required in the patient group at risk.

4. Approach to Management

The approach to managing insomnia involves several steps (see table I). The first step to dealing with sleep difficulties in COPD is to identify the problem. Unless the clinician specifically asks, the problem may remain unrecognised, causing the patient to overemphasis the physical aspects of the disease. Taking a sleep history is not a strength of most physicians,[9] and thus physicians need increased awareness and education in this regard. Understanding the magnitude of the problem allows the clinician to put things in the proper perspective and create a balanced therapeutic approach.

Having characterised the degree and duration of the problem, the clinician should next optimise the general medical management of the COPD since poor symptom and disease control may be associated with poor sleep quality. To that end, optimisation of therapies that have limited systemic effects, such as ipratropium bromide versus sympathomimetics, should be employed.

Where possible, avoidance of drugs known to aggravate insomnia (theophylline, oral corticosteroids) should be made, and history of caffeine consumption should not be overlooked. Salmeterol, a long acting β-agonist (LABA), has been studied in patients with COPD with respect to airflow obstuction but not sleep.[59] As with any therapy the risk-benefit relationship should be considered. If meaningful improvement in pulmonary function can be realised then this may offset any potential adverse effects on sleep. If there is no substantial improvement in pulmonary function, there exists the possibility that sleep may be adversely affected with this therapy. For example, while not thoroughly studied, salmeterol has been observed to cause a deterioration of oxygen saturation in patients with obstructive sleep apnoea by aggravating V/Q mismatch.[60] Although there were no direct adverse effects on sleep quality or apnoea/hypopnoea index, in the long-term the effect of lower oxygen saturation may ultimately result in poorer disease control and more disruption of sleep.

Again, this supports the earlier recommendation that a poorly absorbed therapy such as inhaled ipratropium bromide should be considered as first line therapy in patients who have disrupted sleep given that anticholinergics improve sleep quality and are less likely to aggravate V/Q mismatch than are the sympathomimetics.[61]

Because sleep disturbances are often over long periods of time, much maladaptive behaviour towards sleep may have developed. These behaviours can be identified by a simple sleep history and general suggestions about improving sleep hygiene should always be made (see table II). Behavioural approaches are at least as effective in late-life insomnia in the short-term and superior to temazepam in the long-term.[62] In moderate to severe insomnia, concomitant behavioural treatment (including support of a clinical psychologist) may

Table I. Outline of insomnia management

Identify the problem
Optimise the general management
Search for drugs known to aggravate insomnia
Improve sleep hygiene
Consider pharmacological therapy

be required. Indeed, without adjunctive psychological therapy, hypnotic treatment may quickly become ineffective.

Prior to considering pharmacological treatment, formal assessment of pulmonary function tests and arterial blood gases are required. If these show severe disease, nonpharmacological means are best utilised and drug therapy generally should be avoided. Formal sleep studies may also be indicated depending on perceived risk.

Choice of pharmacological therapy should be guided by the degree of sleep disruption in the context of the severity of the disease. Because the available data applies mostly to COPD patients without hypercapnia, in these patients careful weighing of benefits and risks must be made on an individual basis, with attention to first doing no harm. Even if a patient requires sedation and is deemed at low risk from a safety point of view, a sedating tricyclic antidepressant would seem to be a logical first step. However, in anxious patients with difficulties primarily of sleep initiation, a relatively short-acting benzodiazepine, such as lorazepam, may be quite appropriate. Where sleep maintenance is the problem, newer agents such as zolpidem or zaleplon are better options. Choosing between the two will depend on when in the sleep period is the most troublesome awakening. Because of its shorter half-life, zaleplon can often be given within 4 hours of morning wakening without significant effects on alertness or daytime performance.[63] Even for hypnotics that have little or reduced respiratory depressant effects, extreme caution must be exercised when using these during periods of exacerbation of the underlying lung disease and, in general, they are best avoided in this setting. The one caveat here being patients who are regular, long-term users of sedatives who should have their use minimised but may require small doses of their sedative to avoid withdrawal.

As well following the first prescription of a sedative, follow up should take place to ascertain the tolerability of the medication, specifically questioning about next morning somnolence, stupor or confusion or morning headache (possibly due to hypercarbia) and, in institutionalised patients, measuring oxygen saturation. Once the tolerability of the therapy is determined, the physician can further maximise the benefit to risk ratio by limiting the quantity prescribed and encouraging intermittent (2–3 times weekly) versus regular use. In addition, the patient should be advised to limit or avoid sedatives if they are experiencing more dyspnoea or increased mucus.

5. Conclusions

In summary, it is important to remember that while most hypnotics may work in the short-term, the long-term management of insomnia in patients with COPD will require an integrated approach.

Table II. Elements of good sleep hygiene

Go to bed only when sleepy
Use the bed only for sleeping or sex: it is counterproductive to lay in bed and worry about sleep
Get up at the same time 7 days a week: regular wakening time is the anchor for your intrinsic circadian rhythm: regular wake time leads to regular bedtimes
Regular exercise, in the morning or afternoon, will deepen sleep
Control the bedroom environment to promote sleep: insulate against sound and light and keep the temperature cool enough to sleep
Going to bed hungry or very full can disturb sleep
Avoid excessive liquid intake in the evening to reduce need to go the bathroom after going to sleep
Avoid caffeine-containing drinks (coffee, tea, colas) in the evening
Avoid alcohol in the late evening: even though alcohol can help with falling asleep, sleep is often fragmented
Avoid daytime 'catnaps'
Never 'try' to fall asleep: this only increases frustration and makes it even harder
Remove clocks and other time cues from beside the bed: time pressures are never conducive to a good sleep

Acknowledgements

The authors thank Stacey MacAulay PharmD. for her helpful review of the manuscript.

No funding was received to assist in manuscript preparation. Dr Bayliff has spoken on respiratory related disorders but not regarding the use of sedatives. Dr George has lectured on the use of sedatives in COPD and has participated in two industry sponsored studies.

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