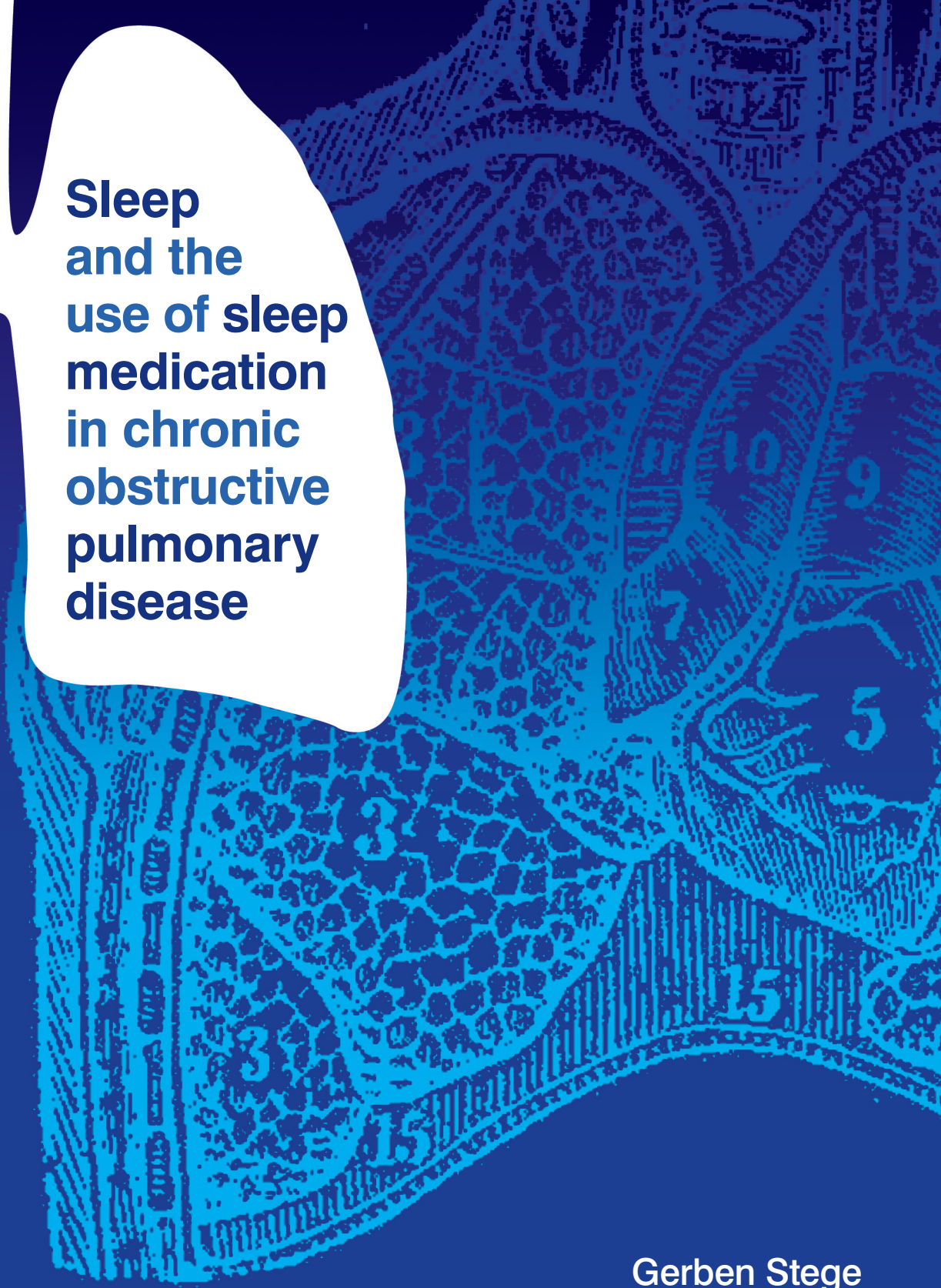
Sleep and the use of sleep medication in chronic obstructive pulmonary disease



Gerben Stege

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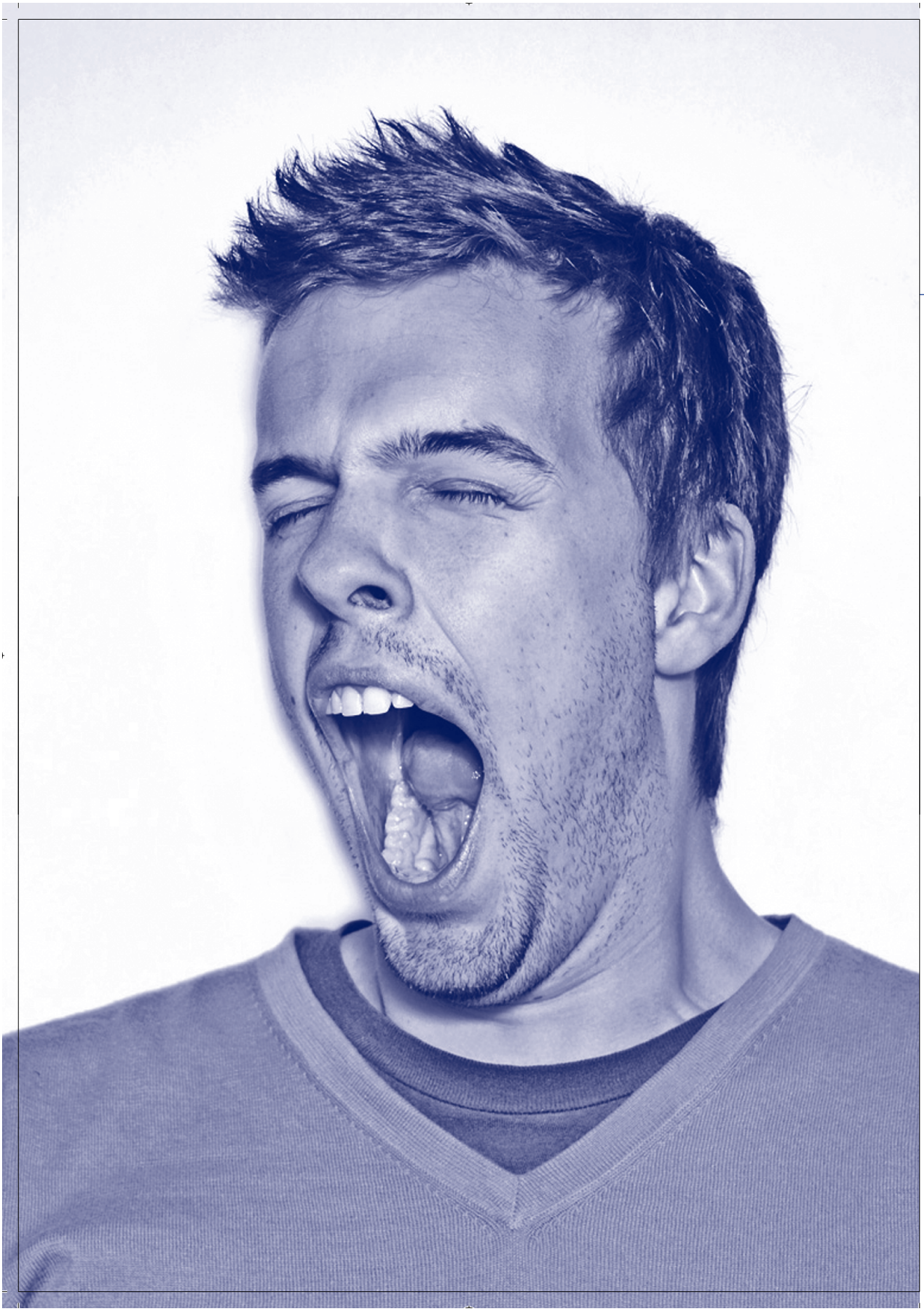

1

Introduction and outline of this thesis

Background

This thesis examines the effects of Chronic Obstructive Pulmonary Disease (COPD) on sleep and the effects of sleep on COPD.

The studies in this thesis describe different aspects of the interaction between COPD and sleep. On the one hand COPD can affect aspects of sleep and on the other hand sleep can have effects on the respiratory function, both in healthy humans and in humans with COPD.

COPD

COPD is a progressive disease, which includes chronic obstructive bronchitis and emphysema and is associated with symptoms as dyspnea, cough and sputum production. The Global initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as 'a disease state characterized by airflow limitation that is not fully reversible,' and which is 'usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases.'[1]

Pathologically, COPD is caused by an inflammatory process within the lungs with abnormal chronic inflammation of airways and lung parenchyma.[2] This results in hypersecretion of mucus and structural changes of the airways (chronic obstructive bronchitis) and in enlargement of air spaces and destruction of lung parenchyma, loss of elasticity and closure of small airways (emphysema).[3]

Tobacco smoking is the main risk factor for the development of COPD. The Lung health study, published in 1994,[4] showed that aggressive smoking intervention significantly reduced the decline in forced expiratory volume in 1 second (FEV_1) in middle-aged smokers with mild airway obstruction.

The severity of airflow obstruction can be classified according to GOLD criteria; GOLD 1 to 4 correspond to respectively mild, moderate, severe and very severe COPD.[1]

The symptoms can be reduced or abolished by inhaled bronchodilators (β-agonists, anticholinergic drugs and methylxanthines) and glucocortisteroids.[5]

The prevalence of COPD is reported to be 9-10%.[6,7] COPD is more and more becoming a public health problem with large consequences. In 2001, it was the fourth leading cause of death in high-income countries,[8] exceeded only by heart attacks, cancers and stroke, and it is the only common cause of death that is increasing in incidence. The World Health Organization expects COPD to rise from its twelfth ranking now to a fifth ranking in 2020 in most prevalent diseases in the world.[9] The reasons for the mentioned increase in mortality are a decrease of mortality due to other diseases like cardiovascular diseases (in industrialised countries) and

infectious diseases (in developing countries), an increase in cigarette smoking and environmental pollution in developing countries and the rise in the ageing population in industrialised countries.[6,10,11]

Furthermore, the impact of COPD on overall mortality is likely to be underestimated because it probably attributes to other common causes of death and the disease is usually only diagnosed when it becomes clinically apparent and moderately advanced.[12]

COPD has a major impact on health status,[13,14] and as the disease progresses lung function and exercise performance will decline and an increase in the frequency of exacerbations is observed.

The overall management goals for COPD are improvement in quality of life and in functional status in the absence of progression of the disease.

Although COPD primarily affects the lungs, it also has significant systemic consequences.[15] With progression of the disease, these systemic effects can become increasingly significant and may have an important negative influence on the quality of life. Systemic effects of COPD include not only weight loss,[16] muscle wasting,[17] cor pulmonale,[18] pulmonary hypertension,[19] excessive fatigue[20] but also sleep-related problems.[20-22]

Sleep quality

Ideally, one falls asleep quickly and easily, stays asleep continuously until awakening the next morning, feeling refreshed and alert. Large inter- and intra-individual variations in sleep quality exist and these variations limit the development of definitions for normal values of sleep quality.

Objective and subjective methods have been developed to assess the (perception of) quality of sleep. An objective method and the gold standard to measure sleep is the polysomnography (PSG). A PSG consists of an electroencephalogram, an electro-oculogram and an electromyogram together with continuous measurements of oxygen saturation, airflow, respiratory effort, limb movements and body position during sleep. Normal sleep is divided into rapid eye movement (REM) sleep and non-REM sleep (nREM), which occur cyclically. NREM sleep is sub classified into stages 1 through 4 and constitutes the bulk of sleep time (approximately 75%). NREM sleep stages 3 and 4 are frequently referred to as deep sleep or slow wave sleep. REM sleep occurs more frequently during the second half of the night and makes up the other 25% of sleep. Sleep stages are classified following the rules developed by Rechtschaffen and Kales.[23] To describe the different stages of sleep, polysomnographic recordings can be graphically summarized in a so called hypnogram (figure 1).

Parameters to describe sleep quality are the total sleep time (TST, defined as the time from the start of sleep until awakening the next morning, minus the time spent

awake during the night), sleep-onset latency (SOL, defined as the time from lying in bed to falling asleep), REM sleep latency, sleep efficiency (SE, defined as the time spent asleep divided by the time spent in bed), the number of arousals, and the amount of REM and non-REM (nREM) sleep stages, as defined by the American Academy of Sleep Medicine (AASM).[24]

Subjective assessments of sleep and daytime sleepiness include numerous sleep diaries[25] and questionnaires (e.g. the Stanford Sleepiness Scale, the Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale).[26,27]

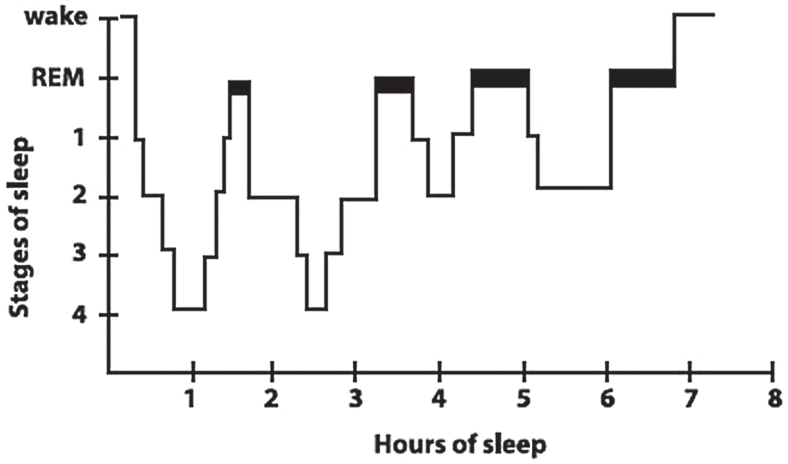

Figure 1 Example of a hypnogram.

This hypnogram shows how a typical night's sleep for a young, healthy adult is organized. Notice how the night is structured into the various stages of non-REM sleep alternating with REM sleep, with most slow-wave sleep occurring in the first part of the night and most REM sleep occurring in the last part.

The physiological regulation of breathing is different during sleep than when awake.[28] For instance, during sleep chemoreceptors function less adequate, cortical input is (obviously) reduced, the respiratory muscle contractility is reduced, and due to the supine position perfusion of the lungs is less favourable during sleep.[29-32] These effects on respiratory regulation can cause hypoventilation followed by hypoxemia and hypercapnia. In healthy humans these changes during sleep have mostly minor consequences and are therefore not harmful. In patients with a pulmonary disease like COPD, sleep can have major adverse effects on the respiratory function.[32,33]

The other way around, COPD has adverse effects on sleep as well. Patients with COPD experience worse quality of sleep than healthy humans.[34-36] Up to fifty-three

percent of COPD patients report sleep-related complaints[22] characterized by a longer sleep latency, more frequent arousals and awakenings, and more daytime sleepiness than healthy individuals. Sleep-related complaints are ranked third in frequency of complaints, after dyspnea and fatigue, by patients with COPD.[20]

Sleep-related complaints

Sleep disorders can generally be divided into four major groups, according to the Diagnostic Classification of Sleep and Arousal Disorders (DCSAD) of the Association of Sleep Disorders Centers (ASDC), published in 1979.[37] These are firstly disorders of initiating or maintaining sleep (i.e. insomnias), secondly disorders of excessive daytime sleepiness (EDS, hypersomnias), thirdly sleep-wake schedule disorders (dyssomnias) and fourthly parasomnias.

Insomnia, the most reported sleep disorder, is defined as difficulty with the initiation, maintenance, duration, or quality of sleep that results in the impairment of daytime functioning, despite adequate opportunity and circumstances for sleep.[38,39] The estimates of prevalence vary within and between countries and range from 10 to nearly 22% in the general population[40,41] and increase with age. Insomnia can be short term (less than a month) or chronic.[38] The subjective complaint may or may not be confirmed by objective evidence from sleep studies or observations by others. Insomniacs may complain of trouble falling asleep, problems staying asleep, such as frequent or prolonged nocturnal awakenings, or early morning awakenings with an inability to resume sleep. The complaint may also be of nonrestorative sleep or diminished sleep quality, resulting in a feeling of being unrefreshed in the morning and low energy during the daytime.

Insomnia is associated with daytime consequences like attention deficits, delayed reaction, memory impairment, functional problems, frequent accidents, and risk of falls.[25,40] Furthermore, patients with sleep problems have higher rates of psychiatric and medical illnesses, and insomnia is an important risk factor in the development of depression, panic disorders and alcohol abuse.[42] Insomniacs also have higher rates of health care utilization[43] and reduced quality of life.[40,41,44,45]

Sleepiness (synonyms: somnolence, hypersomnia) is defined by the AASM as a complaint of difficulty maintaining desired wakefulness or a complaint of excessive amount of sleep.[24] Many patients are thought to underreport their complaints of sleepiness due to habituation and failing to recognise it as pathologic.[46] As well as insomnia, EDS is generally considered to be a major symptom of other sleep disorders, i.e. sleep apnea, or a symptom associated with psychiatric or other medical conditions.

Sleep-wake schedule disorders (like the jet lag syndrome and shift worker syndrome) are also called circadian rhythm sleep disorders and are sleep disorders

that are specifically attributed to dysfunctions or insufficiencies in the circadian system.[47]

Parasomnias are sleep disorders characterized by abnormal behavioural or physiological events which occur during sleep or during sleep-wake transitions. Examples are sleep walking, nightmares, enuresis nocturna and sleep bruxism. Parasomnias typically do not cause insomnia or excessive sleepiness.

Sleep medication use

Sleep-related problems can be treated by behavioural therapies and sleep medication. Because of the side-effects of sleep medication, behavioural therapies are preferred above pharmacological therapies. Sleep medication is only indicated when sleep problems influence daytime functioning and when non-pharmacological therapies remain unsuccessful.

Benzodiazepine-receptor agonists (benzodiazepines and non-benzodiazepine benzodiazepine-receptor agonists (NBBRAs)) are the most common used drugs to promote sleep, but sedating antidepressants and over-the-counter sleep products like antihistamines and melatonin-receptor agonists are used as well. Sleep medication can improve sleep quality but its sedative properties may suppress respiration during sleep.

Assessment of respiratory function during sleep

One of the primary parameters to assess the respiratory function is the partial tension of carbon dioxide (PCO_2). The gold standard in PCO_2 measurements is the arterial measured PCO_2 ($PaCO_2$). However, $PaCO_2$ measurements during sleep have practical disadvantages, like waking someone up when a arterial puncture is performed. An alternative method for $PaCO_2$ is a transcutaneously measured PCO_2 ($PtcCO_2$), which has the advantage that it can be measured continuously via a sensor applied to the earlobe instead of using repeated arterial punctures or an indwelling catheter in an artery (and thus without waking anyone). There are few data on the accuracy of the currently available $PtcCO_2$-sensors.

Drugs to promote sleep

Dutch guidelines advise the use of the benzodiazepines temazepam or nitrazepam as first choice sleeping drugs for insomnia.[48] These drugs are preferred above other sleep promoting drugs because of their efficacy, their intermediate half-life and minimal daytime side effects.[48,49]

Nevertheless, due to their sedative properties temazepam, nitrazepam and other benzodiazepines may suppress respiration. It is unknown whether temazepam (and nitrazepam) causes adverse effects on breathing during sleep in patients with COPD.

Polysomnography

As written above, a PSG is the recording of multiple variables during sleep, including an electroencephalography (EEG), eye movements (electrooculography, EOG), muscle activity (electromyography, EMG), heart rhythm (electrocardiography, ECG), respiratory airflow, respiratory effort and functional saturation of oxygen (SpO_2).

During the study on the effects of temazepam on respiratory function during sleep (chapter 5) PSGs were made. It was noticed that the outcomes of manual analyses of a PSG often differed from outcomes of automated analyses, generated by a software package, of that same PSG. The manual analysis of a PSG is viewed as the gold standard for analysing PSGs.

Research questions

This thesis originated from one clinical question: Do drugs that promote sleep have adverse effects on breathing during sleep in COPD patients? To answer that question a literature search was performed first, which resulted in a review (chapter 2). The search did not provide clear cut answers. Moreover, it brought up even more questions and more studies followed to answer the subsequent questions (chapters 3-6).

This review provides more detailed information on the current knowledge on various topics related to sleep and COPD, like the sleep quality of patients with COPD, sleep-related complaints and their relation to COPD, the effects of sleep on respiratory function in general and in particular in patients with COPD, and the effects of sleep medication on breathing during sleep.

From an epidemiological point of view we assessed the magnitude of the problem of sleep medication and COPD: what was the extent of sleep medication use in patients with COPD? How frequent do patients with COPD use a drug to promote sleep? How

is this use in COPD patients compared to others? And which sleeping drugs are used? To examine the sleep medication use in patients with COPD, a cohort study was performed in four Dutch general practices, comparing the use of sleep medication in COPD patients, patients with another chronic disease (diabetes mellitus) and healthy subjects. This study is presented in chapter 3.

It is assumed that hypoventilation can be expected in patients with COPD when treated with sleep medication. To measure hypoventilation during sleep invasively a $PtcCO_2$ can be used. Because the $PtcCO_2$-sensor has not been validated well, we performed a study to compare the outcomes of $PaCO_2$ and $PtcCO_2$ with each other. Because it would be impossible to do a validation study in sleeping subjects due to the aforementioned disadvantages of arterial punctures during sleep, we chose to measure $PaCO_2$ and $PtcCO_2$ during cardiopulmonary exercise tests (CPET). This study is presented in chapter 4.

The benzodiazepine temazepam is recommended for the (short-term) treatment of insomnia due to its efficacy, intermediate half-life and minimal daytime side effects.[48-50] The effects of temazepam on the respiratory function during sleep had not been examined. A study was conducted with the objective to examine whether prolonged usage of the benzodiazepine temazepam influences indices of breathing and gas exchange during sleep in patients with severe COPD who experience insomnia. This study is presented in chapter 5.

Another study was performed with the objective to assess the accuracy of a automatic system for analyzing PSGs; the outcomes of the automated analysis of sleep and respiratory variables of PSGs were compared to the outcomes of manual analysis in patients with and without COPD. This study is presented in chapter 6.

Chapter 7 contains a summary and a discussion of the main conclusions and recommendations of this thesis and puts them in perspective.

This thesis examines various aspects of the effects of COPD on sleep and vice versa and the following research questions are addressed:

1. What is the current knowledge on a. the sleep quality of patients with COPD, b. the sleep-related complaints and their relation to COPD, c. the effects of sleep on respiratory function in general, d. the effects of sleep on respiratory function in patients with COPD, and e. the effects of hypnotics on breathing during sleep? (chapter 2)
2. What is the rate of hypnotic-use in patients with COPD compared to other patients? (chapter 3)

3. Which sleep medications are used to promote sleep in patients with COPD? (chapter 3)
4. How is the agreement between $PaCO_2$ and $PtcCO_2$ measurements during CPET? (chapter 4)
5. Does prolonged usage of the benzodiazepine temazepam influences indices of breathing and gas exchange during sleep in patients with severe COPD who experience insomnia? (chapter 5)
6. What are the effects of prolonged usage of temazepam on diurnal breathing, gas exchange, and dyspnea in patients with severe COPD and insomnia? (chapter 5)
7. How is the agreement between outcomes of manual analysis of sleep and respiratory variables of PSGs with outcomes of automated analysis in patients with and without COPD? (chapter 6)

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2

Sleep, hypnotics and chronic obstructive pulmonary disease

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Summary

The quality of sleep is significantly compromised in many patients with chronic obstructive pulmonary disease (COPD) and may be further diminished when certain comorbidities are present. A reduced sleep quality is associated with daytime consequences like fatigue, psychiatric problems and an impaired quality of life.

Sleep induces physiologic alterations in respiratory function, which can become pathologic and may provoke or worsen hypoxemia and hypercapnia in COPD. Dyspnea, cough and excessive mucus production should be optimised to minimise causes for sleep disturbance.

Pharmacological therapy may be helpful; sedatives like benzodiazepines and non-benzodiazepine benzodiazepine-receptor agonists (NBBRAs) are (equally) effective in improving sleep quality. Whether or not these hypnotics produce serious adverse respiratory effects during sleep, remains unclear due to opposing studies. Therefore, their use should be as short as possible.

Keywords

Benzodiazepines, breathing, hypnotics, non-benzodiazepine benzodiazepine-receptor agonist, chronic obstructive pulmonary disease, sleep

Abbreviations

COPD	Chronic Obstructive Pulmonary Disease
DIMS	Difficulties Initiating and/or Maintaining Sleep
EDS	Excessive Daytime Sleepiness
FEV_1	Forced Expiratory Volume in 1 second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GABA	Gamma-Aminobutyric Acid
HCVR	Hypercapnic Ventilatory Response
HVR	Hypoxic Ventilatory Response
NBBRA	Non-Benzodiazepine Benzodiazepine-Receptor Agonist
OSAS	Obstructive Sleep Apnea Syndrome
PCO_2	Partial pressure of carbon dioxide
PO_2	Partial pressure of oxygen
REM	Rapid Eye Movement
SaO_2	Oxygen Saturation
TST	Total Sleep Time
V_e	Minute Ventilation
V_i	Inspired minute ventilation
V/Q	Ventilation/perfusion relationships

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease, which encompasses chronic obstructive bronchitis and emphysema and is associated with symptoms such as dyspnea, cough and sputum production. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defined COPD as 'a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients.'[1] Overall, the management goals for COPD are improvement in quality of life and in functional status in the absence of progression of the disease.

Although COPD primarily affects the lungs, it also produces significant systemic consequences, which can have an important negative influence on the quality of life. These systemic consequences include weight loss,[2-4] muscle wasting,[5] cor pulmonale,[6,7] pulmonary hypertension,[8,9] excessive fatigue[10,11] and sleep-related problems.[10,12,13]

This paper reviews the sleep-related problems in patients with COPD and the effects of sleep on respiratory function. The benefits and risks associated with the use of hypnotics in patients with COPD will be discussed.

Sleep quality in patients with COPD

Already in 1976, it was reported that sleep is of poor quality in patients with normoxemic COPD.[14] Several years later, significant disruptions of sleep in patients with hypoxemic COPD were demonstrated in several studies.[13,15,16] These disruptions occurred simultaneously with oxygen desaturations. Total sleep time (TST), amount of rapid eye movement (REM) sleep and slow wave sleep (nREM stages 3/4) were reduced and increases in the number of arousals and in the number of sleep-stage changes per hour were described.[13,16] All these changes in sleep architecture have adverse effects on the sleep quality. Figures 1 and 2 show, respectively, examples of a normal hypnogram and a hypnogram of a patient with COPD and severely disturbed sleep.

The reduction in sleep quality results from a combination of factors. Firstly, dyspnea is exaggerated in the supine position, which causes delayed sleep onset and arousals. Secondly, cough and excessive mucus production may prolong sleep onset, especially because cough and mucus production are exaggerated in the supine position. Thirdly, the supine position results in altered ventilation/perfusion (V/Q) relationships and subsequently nocturnal desaturations and hypercapnia.[17] Fourthly, the increased ventilatory effort that patients with COPD have to deliver in response to hypoxemia and/or hypercapnia, produces awakenings.[18] Fifthly, the nocturnal desaturations and hypercapnic episodes themselves can cause arousals

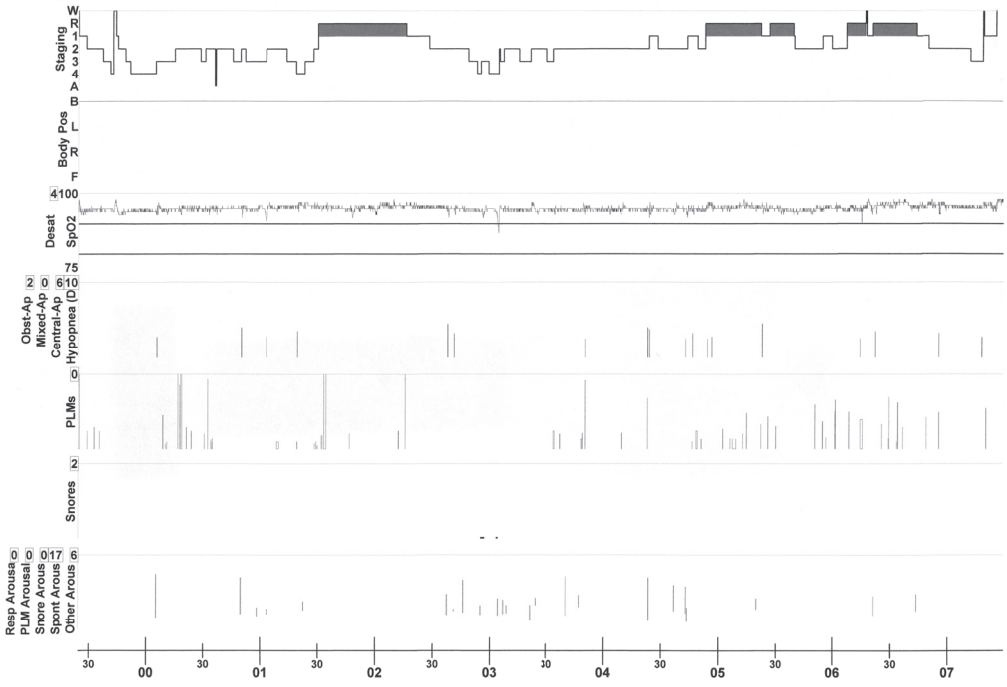

Figure 1 Example of a normal hypnogram.

This hypnogram shows how a typical night's sleep for a healthy adult is organized. Notice how the night is structured into the various stages of non-REM sleep alternating with REM sleep, with most slow-wave sleep occurring in the first part of the night and most REM sleep occurring in the last part.

from sleep. A possible, but uncertain sixth cause is the use of certain pulmonary drugs that might affect sleep, like (oral) corticosteroids,[19,20] β_2-agonists,[21] anticholinergics[22,23] and theophylline.[24] The use of these drugs in patients with sleep complaints will be discussed later on.

Furthermore, it seems that a single night's loss of sleep results in significant, but clinically not relevant reductions of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) in patients with COPD, as was shown by Phillips et al.[25] It is not known whether multiple nights of sleep deprivation affect long-term pulmonary function.

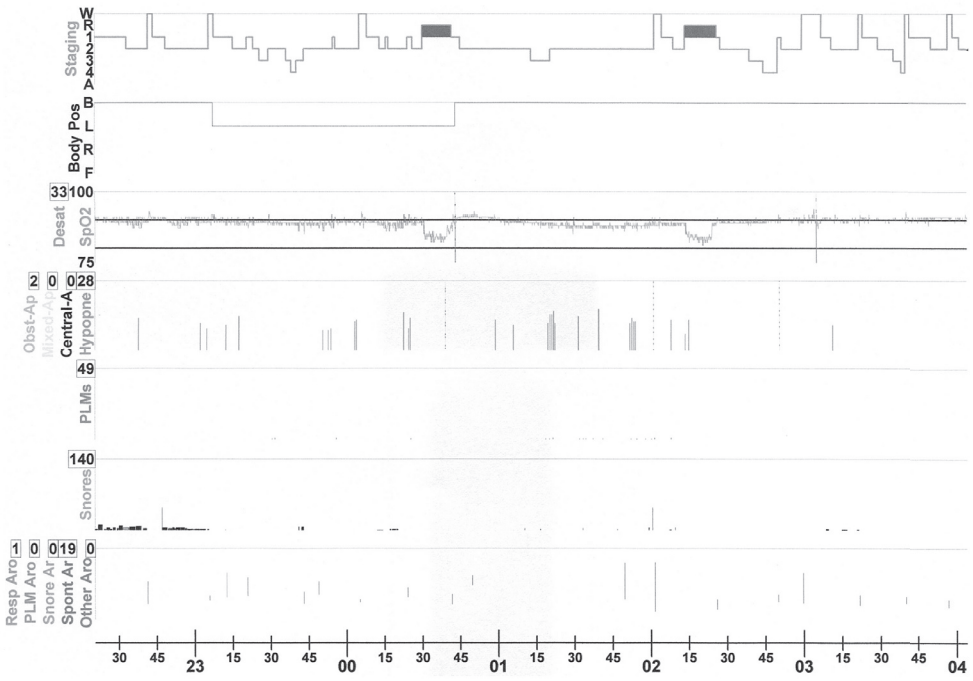

Figure 2 Hypnogram of a patient with COPD and severely disturbed sleep.

Sleep-related complaints in patients with COPD

Insomnia, the most frequently reported sleep disorder, is defined as difficulty falling asleep, difficulty staying asleep, early awakening, or unrefreshing/nonrestorative sleep in an individual who has adequate circumstances and opportunity for sleep.[26] Insomnia is associated with daytime consequences like attention deficit, delayed reaction, memory impairment, functional problems, frequent accidents, and risk of falls.[27,28] Furthermore, patients with sleep problems have higher rates of psychiatric and medical illnesses, and insomnia is an important risk factor for the development of depression, panic disorders and alcohol abuse.[29] Insomniacs also have higher rates of health care utilization[30] and reduced quality of life.[28,31-34]

Sleep-related complaints are ranked third, after dyspnea and fatigue, in frequency of complaints of patients with COPD.[10] No relation was found between pulmonary function and prevalence of sleep-related complaints. In the Tucson Epidemiologic Study of Obstructive Airways Disease[35] it was found that 53% of patients with chronic

bronchitis experienced difficulties initiating and/or maintaining sleep (DIMS) and 26% complained of excessive daytime sleepiness (EDS), compared to 36% and 11%, respectively, in age-matched subjects without any respiratory disease. In addition, further analysis showed that the more pulmonary symptoms a subject experienced during daytime, the higher the rate of sleep complaints was. Also in this study there was no relationship between lung function (FEV_1/FVC ratio) and prevalence of DIMS and EDS.[12]

In another study,[13] patients with COPD (mean FEV_1 0.88 l) also reported more difficulty in getting to sleep and staying asleep and had more daytime tiredness than age-matched controls. Thirty-six percent of COPD patients had trouble falling asleep and 28% of COPD patients reported use of hypnotics compared to, respectively, 15% and 10% of the patients without COPD.[13]

According to ERS/ATS guidelines,[36] all patients with COPD should be questioned about signs of sleep disorders such as EDS, prolonged sleep latency and frequent arousals. Physicians should be alert for the presence of a sleep disorder when one or more of the following problems are present: high blood pressure, breathing problems, urinary problems, depression, chronic pain, and gastrointestinal problems.[37,38]

OSAS should be considered when symptoms like snoring, EDS and witnessed apnea during sleep occur. Other possible causes for insomnia (i.e. comorbidities, drugs) should be explored before any other step is taken to treat insomnia.

In summary, it seems that sleep-related complaints are more prevalent among patients with COPD and that up to 50% of COPD patients experience problems during sleep. The presence of sleep-related problems seems to have no relationship with lung function,[10,12,15] but they may have a relationship with the frequency and severity of pulmonary symptoms.[12] All patients with COPD should be questioned about symptoms of sleep disorders.

Effects of sleep on respiratory function

Sleep induces physiologic alterations in respiratory function, which can become pathologic and may provoke or worsen hypoxemia and hypercapnia. These alterations include changes in the respiratory control centre,[39] in airway resistance,[40,41] in functional residual capacity (FRC),[42] in V/Q relationships[43] and in muscular contractility.[44] During sleep, the respiratory control centre is less sensitive and responsive to chemical, mechanical and cortical input, particularly during REM sleep.[39,43,45] The ventilatory response to hypercapnia and hypoxemia is mainly mediated by “chemical input” from chemoreceptors. Even in healthy persons, the chemoreceptor response is blunted during sleep compared with wakefulness, leading to a modest increase in carbon dioxide tension (PCO_2) of 2 to 6 mmHg and

a marginal decrease in oxygen saturation (SaO_2) of up to 2% from baseline.[46] In healthy adults the airway resistance shows a circadian variation with the lowest resistance around noon and a twofold increase in the early morning (3:00 – 6:00 h a.m.). Airflow resistance rose during sleep in healthy subjects from 3.9 cmH_2O during wakefulness to 7.9 cmH_2O in stage 2 sleep and 8.6 cmH_2O in REM sleep.[40] Peak flow rates drop an average of 8% during the night due to this mild bronchoconstriction.[47] This circadian variation is associated with an increased cholinergic tone during sleep in the airway smooth muscle.[22,48] There is also evidence that an imbalance between both the magnitude and timing of electrical activity between the upper airway and chest wall inspiratory muscles exists during sleep.[49,50] This could cause narrowing of the upper airways. Other mechanisms, like an increase in the levels of inflammatory mediators and steroids during sleep, may also play a role.[51]

Functional residual capacity (FRC) is diminished during both nREM and REM sleep in healthy humans and asthmatic subjects, with the biggest decrease in the latter group.[42,52] The causal mechanism for this decline in FRC is not clear, but a reduced respiratory muscle contractility, cephalad displacement of the diaphragm and a decrease in lung compliance might be responsible.[43] The impact of sleep on FRC in patients with COPD has, to our knowledge, not been studied yet. A reduced FRC results in a closing of small airways and this leads to V/Q mismatching in these areas.[43]

Respiratory muscle function is impaired during sleep, particularly during REM sleep.[44] Ventilation largely depends on diaphragm function during REM sleep, due to reductions in electromyographic activity of the upper airway muscles, intercostal muscles and other accessory muscles during phasic REM sleep compared to non-REM sleep.[53,54] The reduction in the intercostal and other accessory muscle activity leads to a decrease in rib cage contribution to ventilation.[54,55] During REM sleep the ribcage contribution to tidal volume fell from 44% to 19% of the tidal volume.[54] The upper airway dilator muscle function is also compromised, which can cause 'obstructive' hypopnea.[50]

In healthy humans these physiologic changes, and not the respiratory rate, are responsible for a 6% reduction in inspired minute ventilation (V_i) during nREM sleep compared to wakefulness, with a concomitant increase of PCO_2 of 2 – 4 mmHg.[56-59] During REM sleep V_i further decreases by 16% compared to wakefulness.[46]
Similar changes in respiratory function occur during sleep in patients with COPD as in healthy subjects, although some can be more profound in COPD. It was shown that in patients with COPD respiratory control centre output was reduced and upper airway resistance was increased, both most severely during REM sleep.[60] The circadian variation in airflow is exaggerated in patients with COPD.[61-63] A mean daily FEV_1 variation of 286 ml was found, which was a 30% circadian change in FEV_1.[61] A parallel circadian change in FVC was noticed in this study with no meaningful change

in the FEV_1/FVC ratio. The occurrence of V/Q mismatching was suggested following the observation of a relative greater fall in nocturnal SaO_2 than a rise in transcutaneous PCO_2 in some patients with COPD during sleep.[64]

Muscular contractility is already reduced during daytime in patients with COPD and this is aggravated during sleep.[53] The function of the diaphragm is even more decreased than in healthy subjects because it is flattened due to hyperinflation and therefore relatively inefficient.[39] The relatively large dependency on diaphragm function during sleep might explain why patients with loss of respiratory muscle strength show nocturnal desaturations.[65] Sleep has a more pronounced effect on V_i in patients with COPD than in healthy humans. A decrease in V_i of 16% during nREM sleep and a decrease of 32% during REM sleep compared to wakefulness were reported in patients with COPD, whereas the V_i remained practically unchanged during sleep and wakefulness in healthy humans.[59]

In patients with COPD, these changes during sleep may have a more profound effect on gas exchange and can cause severe hypoxaemia and hypercapnia, especially during REM sleep, as was shown by several authors.[14,66-70] One study[68] showed a maximum fall in arterial oxygen tension (PaO_2) of 3.5 kPa during REM sleep in patients with COPD. Another study[69] concluded that disordered breathing during sleep is common in patients with COPD and often causes desaturations (mean desaturation of 7.6% from baseline) due to apneas and hypoventilation. Forty-two percent of the desaturations during sleep could be explained by simultaneously occurring disordered breathing. The prevalence of nocturnal desaturations (SaO_2 drop $>$ 4% from baseline) was present in 78% of the COPD patients in our own study.[70] These desaturations during sleep may be greater than during maximum exercise.[64]

Hypoventilation during sleep in COPD patients, and its consequences on gas exchange, might contribute to the development of chronic daytime hypercapnia, cardiac arrhythmias,[71] myocardial ischemia,[72] pulmonary hypertension,[73] cor pulmonale[74] and even nocturnal death.[75]

Sleep in patients with COPD and comorbidities

Several diseases other than COPD may cause disordered breathing during sleep. When these diseases co-exist with COPD, they have the potential to induce or aggravate hypoventilation during sleep. These are for example the obstructive sleep apnea syndrome (OSAS), neuromuscular disorders like muscular dystrophies, restrictive lung disorders, and cardiovascular disorders like congestive heart failure and atrial fibrillation.

The prevalence of OSAS is not higher in patients with (mild) COPD than in a comparable group of patients without COPD.[76] Therefore, the appearance of COPD and OSAS in one individual (overlap syndrome) appears by chance without any

pathophysiologic linkage. Patients with this overlap syndrome had more severe desaturations during sleep and worse sleep quality than patients with only one of these disorders.[76] They are also more likely to develop pulmonary hypertension,[77] right heart failure[78] and hypercapnia[79] than patients with one disorder.

No data are available on nocturnal respiratory function in patients with COPD and co-existing neuromuscular disorders, restrictive lung disorders or cardiovascular disorders.

Other frequently co-existing diseases or used medication, which do not necessarily influence respiration, may themselves cause or aggravate sleep disorders. These disorders include diabetes mellitus,[80] thyroid diseases, hypertension[81] and psychiatric disorders amongst others. Non-pulmonary drugs which may induce or aggravate sleep disorders are for instance anticonvulsants, analgesics, anti-depressants, beta adrenergic blockers, diuretics, thyroid preparations, caffeine and alcohol.[82]

Physicians should take notice that not only the usage, but also the discontinuation of these drugs may cause sleep disorders.

Treatment of sleep-related complaints

Treatment of sleep-related complaints may vary according to the severity and other co-existing health problems and can be composed of non-pharmacological,[83-85] pharmacological therapy, or both.[86-88]

Non-Pharmacological Therapy

Non-pharmacological therapies produce long-lasting and reliable changes and have minimal side effects in people with chronic insomnia without COPD.[88,89] They include education, sleep hygiene, stimulus control, sleep restriction, relaxation techniques, biofeedback, paradoxical intention and cognitive behaviour therapy.[88] The non-pharmacological management of insomnia concentrated on patients with COPD has not been subject to study yet. Nevertheless, sleep quality in patients with COPD might improve when non-pharmacological therapy is focussed on measures to minimize the previously mentioned causes for sleep disturbance, i.e. on measures to limit dyspnea, cough and excessive mucus production.

In several studies[15,90-92] the effect of oxygen supplementation on sleep quality in patients with COPD was investigated. Two of these studies[90,91] found improvements in sleep quality, where the other two[15,92] did not. Due to methodological differences like randomisation and study populations, these studies are difficult to compare.

Pharmacotherapy

Pulmonary Medication

The β_2-agonist salbutamol did not affect sleep quality and nocturnal oxygenation in patients with asthma and COPD.[21] Studies on the effects of other β_2-agonists on sleep quality are not available. The anticholinergic ipratropium was shown to beneficially influence sleep quality and SaO_2 during sleep in patients with moderate to severe COPD.[22] The number of awakenings per hour of sleep also improved with ipratropium in this study, and the authors discussed that ipratropium might beneficially influence a pre-existing imbalance in the autonomic nervous system which may be the underlying cause for nocturnal dyspnea and sleep disturbance. In another study[23] the long-acting anticholinergic tiotropium improved nocturnal oxygen saturation but did not affect sleep quality. Data on the effects of (inhaled) corticosteroids on sleep are sparse. In one study,[19] a single dose of 60 mg prednisone taken orally reduced the amount of REM sleep and prolonged the REM sleep latency in healthy subjects. Dosages of 5 and 20 mg prednisone had no significant effects on sleep quality in this study. What the effect is of repeated doses of inhaled steroids on sleep is unclear, but in view of its local administration and relatively small amounts, it will perhaps be negligible.

The methylxanthine theophylline has been associated with sleeping complaints due to its chemical resemblance to caffeine (1,3,7-trimethylxanthine). In healthy normal individuals it disturbs sleep quality by prolonging sleep latency, increasing the arousal frequency, reducing TST and increasing the amount of stage 1 sleep.[93,94] Objective studies in patients with COPD[24,95,96] have shown that it does not worsen sleep quality in these patients, and one study[24] even found an improvement in sleep quality. It is likely that the therapeutic effect of theophylline on lung function outweighs the adverse effects on sleep.

In summary, none of the commonly used pulmonary medications are proven to adversely influence sleep quality and the anticholinergic ipratropium may even improve sleep quality.

Hypnotics

Drug therapy is indicated only when sleep-related complaints influence daytime functioning and when non-pharmacologic measures are insufficient to relieve a patient's insomnia. In these cases drug therapy is recommended only for a short period of time. In theory, this means that hypnotics should not be used very often and for 4 weeks maximum. In practice however, hypnotic drugs are frequently prescribed and often on a long-term basis.

The most common medications used to promote sleep are the benzodiazepine receptor agonists (benzodiazepines and non-benzodiazepine benzodiazepine receptor agonists (NBBRAs)). Other agents that are presently used for insomnia include sedating antidepressants and over-the-counter sleep products like antihistamines and melatonin-receptor agonists.

Benzodiazepines and NBBRAs

Some community-based surveys showed benzodiazepines being the most frequently prescribed drug in the general population.[97] Reported prevalence rates of benzodiazepine use range from 2.2% to 17.6%.[98,99] This wide variation in rates can be explained by differences in definitions and observation periods.

There is only one report on the usage of hypnotics in COPD patients.[13] In this study 28% of the COPD patients compared to 10% in the control group (patients with a chronic non-lung disease) regularly used a hypnotic. Other studies on the quantity of prescription of hypnotics, and especially benzodiazepines, in patients with COPD are not available.

Mechanism of Action and Side Effects

In healthy individuals, benzodiazepines improve sleep quality by increasing TST and reducing the latency to sleep onset.[100,101] They affect sleep architecture by increasing the percentage of stage 2 sleep and decreasing the percentage of stages 1 and 3-4 sleep and REM sleep.[102] The precise mechanism of the hypnotic effect is not entirely understood. Benzodiazepines are suspected to bind to the benzodiazepine-receptors (ω-receptors) of the $GABA_a$-receptor-chloride-complex. By doing so, the affinity of this complex for GABA is enhanced. Binding of GABA opens chloride-channels, which causes hyperpolarisation of different cell membranes and subsequently inhibition of neurotransmission, which results in sleepiness, anxiolysis, an anticonvulsant effect and skeletal muscle relaxation. Benzodiazepines differ from each other by their duration of action and pharmacokinetics and can be divided in short-acting (half-life < 5 hrs: brotizolam, triazolam), intermediate-acting (half-life >5, < 24 hrs: temazepam, estazolam, lorazepam, oxazepam) or long-acting (half-life > 24 hrs: nitrazepam, flurazepam, diazepam, quazepam) agents.

NBBRAs like zaleplon, zopiclone and its isomer eszopiclone, zolpidem and alpidem (respectively being a pyrazolopyrimidine, a cyclopyrrolone and the latter two being imidazopyridines) are non-benzodiazepines, which also bind to benzodiazepine-

receptors and exhibit similar effects with some differences from benzodiazepines in pharmacological effects and mechanisms of action. They have short half-lives (3 – 5 hrs) and short durations of action compared with most of the benzodiazepines.

Beneficial Effects

Many randomized trials have shown the efficacy of benzodiazepines[103-106] and NBBRAs[107-111] in relieving short-term insomnia and only in 2003 the first long-term efficacy trial[112] was published. In table 1 the results of different meta-analyses [86,100,101,113,114] are pooled together.

Besides their previously described effects on sleep architecture, benzodiazepines and NBBRAs produce significant improvements in TST, subjective sleep latency, number of awakenings, and subjective sleep quality. Short-acting agents had larger effects on sleep latency than on TST, while the longer-acting benzodiazepines mainly influenced the TST. There was no difference in hypnotic effect between benzodiazepines and zolpidem, although no subgroup-analysis (for short, intermediate- and long-acting drugs) was performed.

In a meta-analysis (n=3909 subjects) the clinical effectiveness of NBBRAs and benzodiazepines was compared.[101] They concluded that there are only minor differences in efficacy between the NBBRAs and between NBBRAs and benzodiazepines, which were difficult to quantify and evaluate, mainly due to limitations in available research.

An interesting observation was noticed by Greene et al.[115] They saw improvements in dyspnea and alertness after alprazolam administration to a 50-year-old male with α_1-antitrypsin deficiency.

Adverse Effects

Besides beneficial effects, all hypnotics show in one way or another unfavourable effects. The previously mentioned meta-analysis[100] reported benzodiazepines to cause complaints of daytime drowsiness, dizziness and light headedness. Other adverse effects include dependence,[116] rebound anxiety and rebound insomnia, memory impairment,[116] withdrawal reactions,[116] a risk of falling associated with muscle hypotonia[117,118] and pneumonia.[119]

NBBRAs show the same range of undesirable effects, and as well as in benefits they show only distinct differences in the magnitudes of adverse effects.[101]

Furthermore, benzodiazepines and NBBRAs have extensively been studied for their effects on breathing during sleep, both in healthy individuals (table 2), in patients with COPD (table 3) and once in elderly patients with sleep apnea.[120] Most, but not all studies were performed during sleep. Medications studied included alprazolam,[115]

Table 1 Findings of meta-analyses regarding the efficacy and safety of benzodiazepines and NBBRAs

Source	No. of subjects	Age (years)	Compared drugs	Main conclusions
Dündar et al.[101]	3909	*	Benzodiazepines NBBRAs	• All short-acting hypnotics are equally effective for insomnia • Equally safe • Only minor differences between the drugs, probably due to pharmacokinetics
Glass et al.[113]	1072	>60	Antihistamines Benzodiazepines NBBRAs	When compared to placebo, sedatives • produced significant but small improvements in sleep quality • gave more adverse effects (NNT: 6 for adverse effects)
Holbrook et al.[100]	2672	29-82	Antihistamines Benzodiazepines Gluthetimide Zopiclone	When compared to placebo, sedatives • improved sleep quality (TST increased 62 minutes) • gave more adverse effects (OR 1.8) When compared amongst one another, • benzodiazepines and zolpidem are equally effective and safe
Nowell et al.[114]	1894	18-65	Benzodiazepines Zolpidem	When compared to placebo, sedatives • improved objective and subjective sleep quality • adverse effects*
Smith et al.[86]	470	47.2	Benzodiazepines NBBRAs	When compared to placebo, sedatives • improved objective and subjective sleep quality When compared with behavioural therapy, sedatives • showed comparable efficacy Adverse effects*

NBBRA, non-benzodiazepine benzodiazepine receptor agonist; NNT, number needed to treat; NS, not significant; OR, odds ratio; TST, total sleep time. *Not reported.

Table 2 Findings of studies regarding the adverse effects of benzodiazepines and NBBRAs in healthy subjects

Source	No. of subjects	Drug, dose	Length of drug use	Conclusions
Beaumont et al.[139]	12	Zaleplon Zolpidem	1 night	• No AE on respiration
Beaumont et al.[140]	8	Zolpidem	1 night	• No AE on respiration
Berry et al.[136]	6	Triazolam 0.25 mg	1 night	• AE on arousal threshold
Cohn[121]	12	Brotizolam 0.5 mg	6 h	• No AE on circulatory and respiratory parameters (pulse, blood pressure, FEV_1, FVC, respiratory rate, mouth occlusion pressure and HCVR)
Cohn[142]	12	Zolpidem 10,20 mg Codeine phosphate 60 mg	3 h	• AE: 20 mg zolpidem decreased inspiratory flow • No AE on respiratory parameters after 10 mg zolpidem • AE: codeine phosphate decreased HCVR and mouth occlusion pressure
Dolly and Block[130]	20	Flurazepam 30 mg	1 night	• AE on SDB and SaO_2-levels
Maillard et al.[123]	16	Diazepam 10 mg Zolpidem 10,20 mg	3 h	• No AE on V_t and mouth occlusion pressure
Mak et al.[124]	6	Diazepam 5 mg Midazolam 7.5 mg	1 h	• No AE on V_e, HCVR and HVR
McCann et al.[141]	10	Zolpidem 10 mg	1 night	• No AE on RDI and SaO_2-levels
Ranlov and Nielsen[125]	10	Diazepam 10 mg Zopiclone 7.5 mg	1 day	• HCVR reduced after diazepam, not with zopiclone • No AE in ABG, V_t, V_e and breathing frequency
Schneider et al.[102]	24	Triazolam 0.25 mg Flunitrazepam 2 mg	1 night	• No AE on RDI and desaturation-index • Increase in breathing frequency • Increase in oesophageal pressure

AE, adverse effects; ABG, arterial blood gas; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCVR, hypercapnic ventilatory response; HVR, hypoxemic ventilatory response; RDI, respiratory disturbance index; SaO2, arterial oxygen saturation; SDB, sleep-disordered breathing; Ve, minute ventilation; Vt, tidal volume.

Table 3 Overview of studies regarding the adverse effects of benzodiazepines and NBBRAs in patients with COPD

Source	No. of subjects	Severity of COPD	Drug, dose	Length of drug use	Conclusions
Beaupre et al.[122]	32	Moderate to severe	Diazepam Zopiclone	1 day	• AE: diazepam increased PetCO2 • AE: zopiclone increased breathing frequency • No differences between the two drugs
Block et al.[128]	20	FEV1 1–2 l	Flurazepam 30 mg	1 night	• AE on SDB and SaO2-levels
Cohn et al.[127]	29	Mild	Flurazepam 30 mg Estazolam 2 mg	5 days	• AE: flurazepam decreased Vt and SaO2 and increased breathing frequency • No AE on HCVR
Cummiskey et al.[129]	5	Mild	Flurazepam 15 and 30 mg	7 nights	• No AE on respiratory parameters
Girault et al.[143]	10	Mean FEV1 0.84 l	Zolpidem	9 nights	• No AE
Greene et al.[115]	1	Mild	Alprazolam 0.5 mg	8 h	• Case report: no AE on respiratory parameters
Jolly et al.[134]	9	Mean FEV1 0.9 l	Lorazepam 1.5–2 mg	1 h	• AE on VE and respiratory muscle strength
Midgren et al.[133]	14	*	Nitrazepam 5 mg Flunitrazepam 1mg	1 night	• No AE on respiratory parameters
Muir et al.[144]	6	Severe	Zopiclone		• No AE on respiratory parameters
Murciano et al.[132]	9	Severe	Triazolam 0.25 mg Flunitrazepam 1mg Zolpidem 10 mg	2 h	• AE: flunitrazepam increased PaCO2 and decreased Ve • No AE on ABG, mouth occlusion pressure, HCVR with triazolam and zolpidem

Table 3 Continued

Source	No. of subjects	Severity of COPD	Drug, dose	Length of drug use	Conclusions
Murciano et al.[131]	12	Mean predicted FEV1 32%	Triazolam 0.25 mg Flunitrazepam 1mg Zolpidem 10 mg	2 h	• No AE on ABG, mouth occlusion pressure, HCVR with zolpidem • AE: flunitrazepam and triazolam increased PaCO2 and decreased Ve
Rudolf et al.[135]		*	Nitrazepam 10 mg	Repeated nights	• AE: increase PaCO2 in hypercapnic patients
Steens et al.[137]	24	Mean predicted FEV1 61%	Triazolam 0.25 mg Zolpidem 5 and 10 mg	1 night	• No AE on SaO2 and RDI • No differences between triazolam and zolpidem
Timms et al.[138]	10	FEV1 17–76%	Triazolam 0.125 and 0.25 mg	1 night	• No AE on desaturation-index and RDI
Wedzicha et al.[126]	9	*	Diazepam 5 mg	1 night	• Sleep duration improved • No AE on nocturnal hypoxaemia and the number of apneic events

ABG, arterial blood gas; AE, adverse effects; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1s; HCVR, hypercapnic ventilatory response; PaCO2, arterial carbon dioxide tension; PetCO2, end-tidal carbon dioxide tension; RDI, respiratory disturbance index; SaO2, arterial oxygen saturation; SDB, sleep-disordered breathing; Ve, minute ventilation; Vt, tidal volume. *Not reported.

brotizolam,[121] diazepam,[122-126] estazolam,[127] flurazepam,[127-130] flunitrazepam,[102,131-133] lorazepam,[134] midazolam,[124] nitrazepam,[133,135] temazepam,[120] triazolam,[102,131,132,136-138] zaleplon,[139] zolpidem,[123,131,132,137,139-143] and zopiclone.[122,125,144]

Some of these studies (using diazepam, flunitrazepam, flurazepam, lorazepam, nitrazepam, triazolam, zolpidem, and zopiclone) found that these drugs decrease central respiratory drive, increase upper airway resistance, particularly by acting on upper airway dilators (genioglossus muscles), decrease the arousal response, decrease respiratory muscle strength, and increase sleep-disordered breathing. Adverse effects were expressed as an increase in the number of apneas, prolongation of occurring apneas, increase in the degree of desaturation, depression of the CO_2 ventilatory response, increase in breathing frequency, prolongation of the time to arousal following airway occlusion, and increase in respiratory effort (according to rise in end-expiration oesophageal pressure).

These unfavourable effects were present both in healthy subjects and patients with COPD, and although most results were significant, the magnitudes were small.

Opposing results, again present both in healthy subjects and patients with COPD, are available from a comparable amount of other studies[120,121,123,124,126,129,133,137,138,140] (table 2 and 3). These studies also focused on the respiratory effects of hypnotics (using alprazolam, brotizolam, diazepam, midazolam, flunitrazepam, flurazepam, nitrazepam, zaleplon, zolpidem, zopiclone), but could not find any adverse effects. Although Steens et al.[137] found no differences in arterial oxygen saturation and apnea-hypopnea-index after zolpidem, triazolam or placebo use in 24 subjects with COPD (mean FEV_1 61%), they felt that 'caution is still required when these hypnotics are prescribed to these patients.'

Several problems occur when interpreting these studies. One problem with most of these studies is their limited duration. Due to short study periods of only a few nights or even only one night, carry-over effects were often not measured. A second problem is the inclusion of subjects with a varying severity of COPD. Thirdly, none of the available studies was performed in COPD patients while they had an exacerbation, although it could be hypothesised, that during an exacerbation more severe sleeping problems exist. A fourth problem is the use of different benzodiazepines with different pharmacodynamics, which makes these studies even more difficult to compare. Moreover, various respiratory parameters have been used to evaluate respiratory function, what makes the comparison also more troublesome.

None of these studies mention the presence or absence of sleep-related problems in their subjects, so it is not known if these results can uniformly be applied to patients with and without sleep-related problems and those with sleep-related problems are precisely the patients one might prescribe a hypnotic to. Furthermore, only one study[127] evaluated effects (adverse as well as beneficial) of ante noctem benzodiazepines during daytime.

Benzodiazepines vs. NBBRAs

Six studies[122,123,125,131,132,137] compared the respiratory effects of NBBRAs and benzodiazepines with each other. Five of these studies were performed in patients with COPD and three of these[122,131,132] reported adverse respiratory effects. Only one author found in two similar studies that a long-acting benzodiazepine (flunitrazepam increased $PaCO_2$ and decreased V_E) had more unfavourable effects on respiration than a short-acting benzodiazepine (triazolam) and a NBBRA (zolpidem). The other four studies all reported no differences in adverse respiratory effects between benzodiazepines and NBBRAs. To date, a meta-analysis on this subject has not been carried out, but could be helpful to interpret these contrasting reports.

Alternative Sedatives

Sedating antidepressants, antihistamines, melatonin and other over-the-counter drugs like 5-hydroxytryptophan, St. John's Wort and valerian root are sometimes used in the treatment of insomnia. The use of these alternatives rather than benzodiazepines and NBBRAs for the pharmacological treatment of insomnia is not supported by available evidence in healthy subjects or in patients with COPD.[145,146] The occurrence of respiratory adverse effects associated with these drugs has been subject of a few studies,[147-149] but without evidence for their efficacy in insomnia, more of these studies will probably not be needed.

Discussion and Conclusion

Overall, one can conclude that (a) NBBRAs and benzodiazepines both improve sleep quality, whereas alternative hypnotics fail to do so; (b) NBBRAs and benzodiazepines seem to be equally effective in treating insomnia; (c) short-acting agents mainly improve subjective and objective sleep latency while longer acting agents mainly improve TST; (d) all NBBRAs and benzodiazepines can produce undesirable effects like drowsiness, dependence, rebound insomnia and memory impairment; (e) regarding adverse effects only distinct differences exist between NBBRAs and benzodiazepines; (f) in healthy subjects four studies reported modest adverse respiratory effects associated with benzodiazepines and NBBRAs, where six other studies did not; (g) seven studies with patients with COPD showed adverse respiratory effects associated with NBBRAs and benzodiazepines, where seven others did not; (h) comparison studies showed no significant differences in benefits and adverse effects between short acting benzodiazepines and NBBRAs but more adverse effects were seen with longer acting benzodiazepines.

Obviously, a meta-analysis is needed but is difficult to carry out due to the wide variation in available studies. Benzodiazepines may have some adverse effects on

respiratory function in healthy people, although these effects may only be very moderate and therefore could be tolerated in this population. Comparable changes are seen in patients with COPD, but it remains unclear if these can be tolerated as well. Consequently, the use of benzodiazepines in these patients should be as short as possible.

ERS/ATS guidelines[36] state that 'hypnotics, particularly benzodiazepines, should be avoided, if possible, …, although there is evidence that some hypnotics, such as zolpidem, can be used in less severe COPD without significant adverse effects on gas exchange.' This statement is partially in contrast to the findings in this review, because (a) several studies failed to show deleterious effects on respiration from hypnotics and (b) as written above, comparison studies showed no significant differences between short acting benzodiazepines and NBBRAs.

Physicians should keep in mind that up to 50% of their patients with COPD experience sleep abnormalities. By asking for sleeping complaints and understanding the pathophysiology and available treatment options for these problems, they have a great tool to substantially improve their patients' quality of life. Therefore more research is needed on the usage of sleep medication in patients with COPD.

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Conflict of Interest Statement

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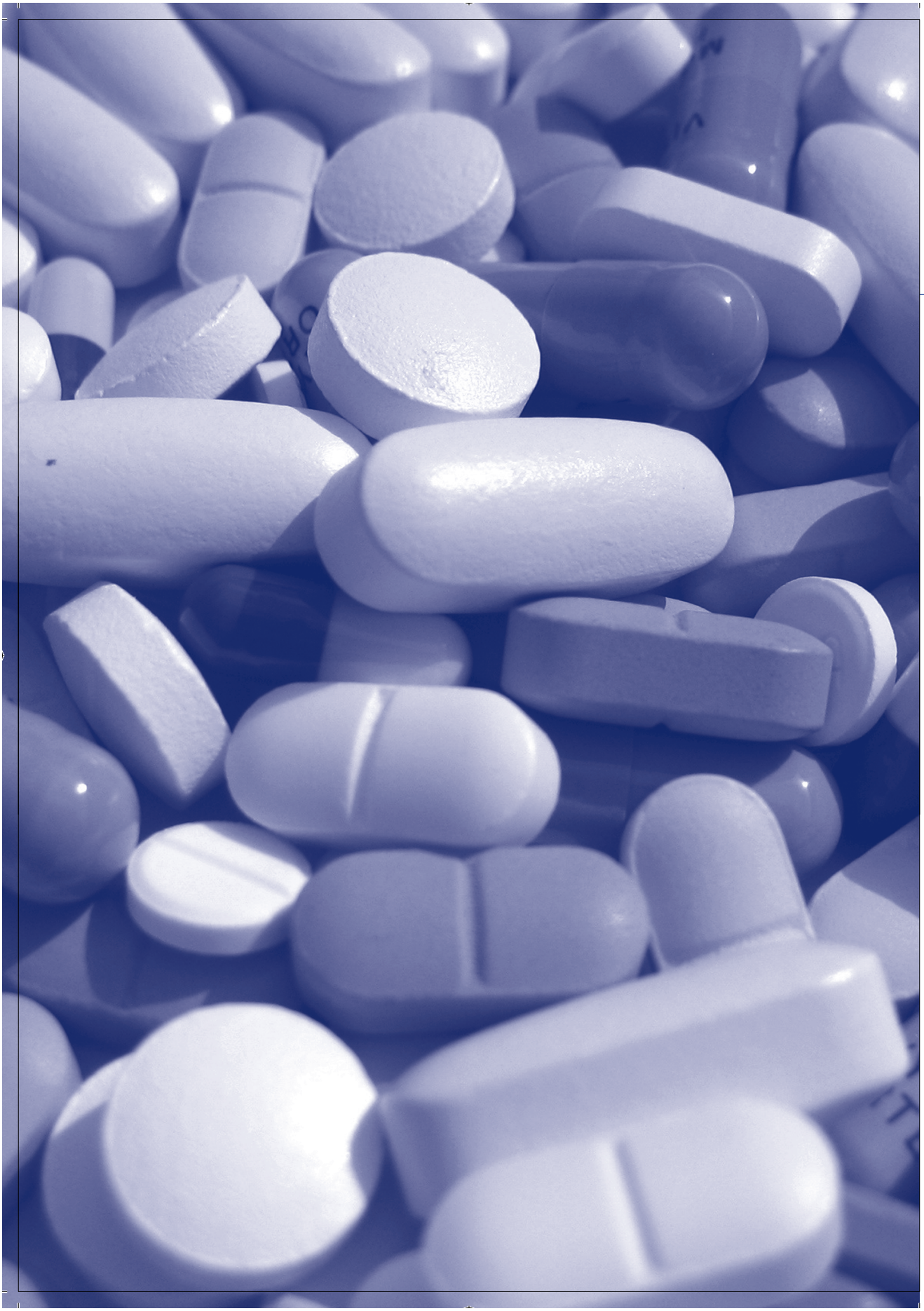

3

The use of sleep medication in patients with COPD in primary care

Submitted

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Abstract

Background Sleep medication may have adverse effects on breathing in COPD patients, but it is unclear to what extent patients with COPD use hypnotics.
Objective: to assess the rate of hypnotic-use in patients with COPD.
Methods In a prospective, observational cohort study in four general practices in the Netherlands we selected patients with COPD, a healthy control group, and a control group of patients with diabetes mellitus (DM) and assessed if and when each patient had been prescribed a hypnotic. Chi-squared tests and Cox proportional hazard analysis with correction for possible confounders were used to compare the prescription of hypnotics in these three groups.
Results From a cohort of 1,078 patients, 176 COPD patients, 176 healthy controls and 291 DM patients were included. 21.6% of the COPD group had ever used a hypnotic compared to 19.3% and 17.2% of the healthy control group and DM group respectively (p=0.50). After adjusting for age, gender, socioeconomic status and co-morbidities, the hazard ratio for prescribing a hypnotic for the COPD group compared to the healthy control group was 1.29 (95% CI 0.80-2.10) and compared to the DM group 1.39 (95% CI 0.90-2.16).
Conclusion The prescription of hypnotics is frequent in patients with COPD but similar to healthy subjects and patients with DM in this primary care population.

Keywords
Epidemiology, hypnotics and sedatives, primary health care, chronic obstructive pulmonary disease, sleep disorders

Abbreviations

CI	Confidence Interval
CMR	Continuous Morbidity Registration
COPD	Chronic Obstructive Pulmonary Disease
DM	Diabetes Mellitus
FEV1	Forced Expiratory Volume in one second
GP	General Practitioner
HR	Hazard Ratio
ICHPPC	International Classification of Health Problems in Primary Care
NBBRA	Non-Benzodiazepine Benzodiazepine Receptor Agonist
NHG	Nederlands Huisartsen Genootschap (Dutch General Practitioner Association)
OR	Odds Ratio
SES	Socioeconomic Status

Introduction

Patients with chronic diseases in general and patients with chronic obstructive pulmonary disease (COPD) in particular experience higher rates of sleep problems than healthy individuals (odds ratio (OR) 1.6).[1-7] Sleep problems are ranked third, after dyspnea and fatigue, in frequency of complaints of patients with COPD,[8] and sleep quality, objectively measured by polysomnographic recordings, can severely be diminished in these patients.[6,9,10]

General practitioners (GPs) can frequently encounter these sleep problems and consequently be asked to prescribe a hypnotic to a patient with COPD. The American Thoracic Society/European Respiratory Society guidelines advise not to prescribe hypnotics to patients with COPD[11] because they may cause adverse effects on respiration (i.e hypoventilation).[12]

Despite these guidelines GPs do prescribe sleep medication to patients with COPD who present themselves with sleeping problems, perhaps because non-pharmacological remedies are not always successful.[13] And although many papers are written on the pros and cons of sleep medication in patients with COPD, the extent of its use in these patients has not been well studied.

Therefore, the primary objective of this study was to assess to what extent patients with COPD are prescribed hypnotics. We also investigated how prescription rates of hypnotics in COPD compare with prescription rates in patients with diabetes and healthy subjects. Since probably most patients with COPD primarily present their sleeping problems to their GP, a primary care population was studied.

Methods and materials

Design

This investigation was a cohort study with a dynamic population (i.e. with new subjects entering and others leaving as time passed), based on a database with a 37-year observation period: the Nijmegen Continuous Morbidity Registration (CMR), an academic general practice network in the Netherlands. Details of the CMR-database have been described elsewhere.[14] In brief, the CMR-database was established in 1971 and records all new episodes of morbidity in all patients of four general practices in the surroundings of Nijmegen, the Netherlands. Morbidity is registered when it is presented to a general practitioner (GP) or when a diagnosis is made after referral to a specialist. Episodes of morbidity are entered in the database linked to a patient-identity code, unique for every individual patient in the practices. The patient-identity code provides demographic characteristics: gender, age and SES. SES is grouped into low (unskilled and skilled manual workers), middle (lower employees) or upper class (higher employees), according to patient's occupation.[15]

The practices have a stable practice population of approximately 12,000 individuals, with an annual turn over rate of 5%. Given the structure of the Dutch health care system, this cohort is representative of the Dutch population in terms of age, gender and social class.[16]

All patients of the practices were informed of the use of their data for research and asked to provide written consent. Only anonymous information of the patients was used. Since only information already available was used, no approval of an internal review board was needed.

Subjects

All patients in the CMR-database with physician-diagnosed COPD or diabetes mellitus (DM) since 1995 and an age above 40 years at the time of diagnosis were included. In 1995 the GPs in the CMR-practices started using spirometry in the diagnostic approach of COPD.[17] Patients younger than 40 years at the time of their initial diagnosis of COPD were excluded in order to avoid misdiagnosis of COPD for asthma. We selected patients with DM type 1 or type 2 as a reference group of patients with another common chronic disease. Subjects in the 'healthy' control group were also selected from the CMR-database.

Patients were excluded when the date of diagnosis was unknown or was before 1995 (because of lack of a spirometry-confirmed diagnosis), when information on at least one of the selected covariates (age, gender, socioeconomic status (SES), co-morbidities) was missing, when they had used sleep medication prior to the date of diagnosis, when they had had a condition other than a sleep problem in which sleep medication is used (like anxiety disorders, depression, epilepsy), or when they had been diagnosed with both COPD and DM. All subjects in the control groups who were matched with someone with one of the exclusion criteria were excluded as well.

Definitions

COPD was diagnosed following the COPD guidelines issued since 1992 by the Dutch College of General Practitioners (NHG),[18] and GPs used the International Classification of Health Problems in Primary Care (ICHPPC-2)[19] to classify a diagnosis.

Drugs that were classified as sleep medication were the benzodiazepines, the non-benzodiazepine benzodiazepine receptor agonists (NBBRAs), and sedating anti-depressants.

The SES was classified as low, middle or high, according to previous publications. For each healthy control subject, a dummy 'date of diagnosis' was used that equaled

the date of COPD diagnosis of the patients with COPD to whom they were matched. This fictitious 'date of diagnosis' meant that controls had to be present in the CMR database at the same moment in time when an COPD diagnosis was given to their matched patient with COPD. This accounted for any possible time period effect in diagnoses of COPD. The dummy date of diagnosis marked the start of the observation period for the controls. Follow-up ended (i.e. data were censored) for each individual subject at the date of first prescription of a hypnotic, the date the patient left the CMR practice or the selected date of study termination (1 January 2009), whichever occurred first.

Potential confounders in terms of co-morbid conditions for the statistical analysis were derived from studies on co-morbidities in patients with COPD.[7,20] These potential confounders were sinusitis, decompensatio cordis, angina pectoris, atrial fibrillation, myocardial infarction, joint pain, migraine, gastric- and duodenal ulcers, neoplasm and cor pulmonale.

Measurements and outcomes

All patients with COPD who met the inclusion criteria were identified from the CMR-database and matched for age, gender, and SES to a patient with DM and to a healthy subject from the same cohort. We used 'greedy' propensity matching scoring, balancing the covariates age, gender, SES, and general practice in the propensity score model, with a variable number (1, 2, or 3) of control subjects for each patient with COPD.[21] In other words, for each patient with COPD, a maximum of three control subjects were selected, who had the same risk of using sleep medication based on the aforementioned covariates.

The use of sleep medication was retrieved from each patient's medical files, including the following details: if someone had used sleep medication, the drug that was prescribed, and the date of its first prescription since diagnosis of COPD or DM. The presence of an anxiety disorder, depression, epilepsy, and any other co-morbidity was recorded as well.

Analysis

The prescription-rate of hypnotics in patients with COPD, DM and healthy individuals was calculated, and the Chi-squared test was used to compare these results with each other. Cox proportional hazards analysis was performed to calculate the hazard ratio (HR) for hypnotic use in patients with COPD compared to the healthy control group and to the DM group. These HRs were calculated in order to describe the risk

of sleep medication use in the three study groups. HRs are presented with 95% confidence intervals (CI). Separate models were made for the hazard of COPD vs. the control group and COPD vs. the DM group. Here, the presence of COPD, DM or the absence of COPD was the independent variable, and the first prescription of sleep medication the dependent variable. Age, gender, SES and co-morbidities were added as covariates to the models, where the occurrence of co-morbidities during the observation period was treated as a time-dependent variable in the Cox analyses. A hazard chart for using a hypnotic in the three groups was also made using Cox proportional hazard analysis.

P-values less than 0.05 were considered statistically significant. Data analyses were conducted using SPSS (version 17.0; SPSS, Chicago, IL).

Results

Subjects

The flow diagram in figure 1 shows the selection procedure of the three study groups. A total of 1,078 patients with COPD was initially identified from the available cohort of an average of approximately 12,000 individuals throughout the observation period. After applying the exclusion criteria, final analyses were based on 176 COPD patients, 291 DM patients and 176 healthy controls.

The characteristics of the subjects are shown in Table 1. There were no statistically significant differences between the three groups in respect to age, sex and SES.

Outcomes

The use of sleep medication in these groups is shown in Table 2. There were no statistically significant differences in sleep medication use between patients with COPD vs. healthy controls and patients with COPD vs. DM (respectively 21.6% vs.17.2 % and 21.6% vs. 19.3%, $p = 0.50$).

The mean duration to the first prescription of sleep medication was 5.3 ± 3.5 years for the COPD group, 5.7 ± 3.5 years for the control group and 5.0 ± 3.4 years for the DM group.

Hypnotics that had been prescribed to COPD patients were temazepam (16 times), oxazepam (13 times), diazepam (5 times), zolpidem (twice), clobazam and alprazolam (both once). These types and frequencies of prescribed drugs did not differ statistically significantly from the other two study groups.

Hazard ratios for prescribing a hypnotic were 1.29 (95% CI 0.80 – 2.10) in COPD vs. healthy controls and 1.39 (95% CI 0.90 – 2.16) in COPD vs. DM. (shown in Table 3

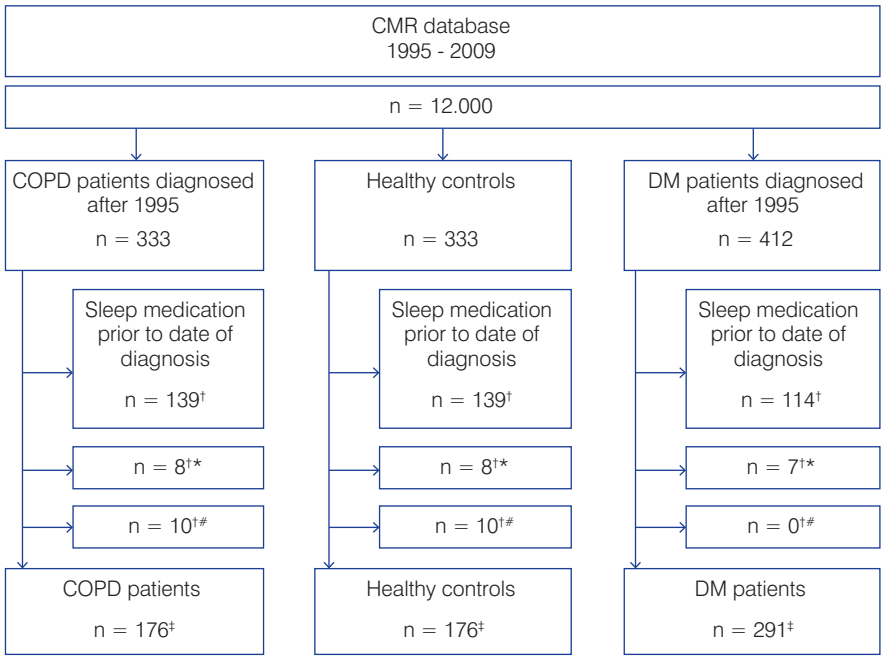

Figure 1 Flow diagram of selection of COPD cases, DM cases and healthy controls from the CMR-database

CMR Continuous Morbidity Registration; COPD Chronic Obstructive Pulmonary Disease; DM Diabetes Mellitus. † matches were excluded when the subjects they were matched to were excluded; * excluded for having one of the co-morbidities anxiety disorder, depression, or epilepsy; # excluded for missing data; ‡ included in main analysis.

Table 1 Characteristics of the subjects

	COPD	Healthy controls	DM
No. of subjects	176	176	291
Sex (M)	115 (65)	112 (64)	165 (57)
Mean age ± SD, years	69,5 ± 13,9	69,1 ± 13,8	70,4 ± 11,7
SES			
low	71 (40)	73 (41)	143 (49)
middle	81 (46)	80 (45)	118 (41)
high	24 (14)	23 (14)	30 (10)

Values are expressed as n (%), unless stated otherwise. COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; SES: socio-economic status.

Table 2 Use of sleep medication in patients with COPD, patients with DM and healthy controls

	COPD n=176	Healthy controls n=176	DM n=291	P-value
Use of sleep medication	38 (21.6)	34 (19.3)	50 (17.2)	0.50
Time to first use of sleep medication, years	5.3 ± 3.5	5.7 ± 3.5	5.0 ± 3.4	0.11

Data are expressed as n (%) or mean ± SD. COPD: Chronic Obstructive Pulmonary Disease; DM: Diabetes Mellitus.

and Table 4). After adjusting for the potential confounders age, SES, gender, and the presence of a co-morbidity, only age was a statistically significant confounder in the multivariate Cox regression model.

Table 3 Hazard ratios of Cox proportional hazard regression model for sleep medication use in patients with COPD compared to healthy controls and adjusted for possible confounders

Variable	Hazard ratio	95% CI	P-value
COPD vs. healthy controls	1.29	0.80 – 2.10	0.30
Socioeconomic status*			
Middle vs. others	1.01	0.56– 2.43	0.98
High vs. others	1.19	0.51 – 2.80	0.69
Gender			
Male vs. female	0.66	0.39 – 1.11	0.12
Age	1.02	1.00 – 1.05	0.04
Co-morbidities			
Weeks with co-morbidity vs. weeks without co-morbidity (time-dependent covariate)			
Sinusitis	0.00	0.00 – 0.00	0.96
Decompensatio Cordis	1.22	0.40 – 3.67	0.73
Angina Pectoris	1.11	0.46 – 2.64	0.82
Atrial fibrillation	2.23	0.79 – 6.31	0.13
Myocardial infarction	1.08	0.41 – 2.83	0.87
Joint pain	1.72	0.59 – 5.04	0.32
Migraine	1.37	0.33 – 5.82	0.67
Gastric- and duodenal ulcers	1.66	0.47 – 5.81	0.43
Neoplasm	1.29	0.56 – 2.97	0.56
Cor pulmonale†	-	-	-

* Reference group: low socioeconomic status.
† This co-morbidity did not occur in any of the study subjects.

Table 4 Hazard ratios of Cox proportional hazard regression model for sleep problems in patients with COPD compared to patients with DM and adjusted for possible confounders

	Hazard ratio	95% CI	P-value
COPD vs. DM	1.39	0.90 – 2.16	0.14
Socioeconomic status*			
Middle vs. others	1.57	0.70 – 3.54	0.28
High vs. others	1.35	0.58 – 3.12	0.49
Gender			
Male vs. female	0.76	0.48 – 1.19	0.23
Age	1.02	1.00 – 1.04	0.05
Co-morbidities			
Weeks with co-morbidity vs. weeks without co-morbidity (time-dependent covariate)			
Sinusitis	0.00	0.0 – 0.00	0.96
Decompensatio Cordis	0.92	0.39 – 2.17	0.86
Angina Pectoris	1.54	0.80 – 2.97	0.20
Atrial fibrillation	1.96	0.93 – 4.11	0.08
Myocardial infarction	0.78	0.37 – 1.61	0.49
Joint pain	1.46	0.52 – 4.07	0.47
Migraine	0.46	0.06 – 3.40	0.45
Gastric- and duodenal ulcers	1.63	0.57 – 4.63	0.36
Neoplasm	0.97	0.44 – 2.14	0.95
Cor pulmonale†	-	-	-

* Reference group: low socioeconomic status.
† This co-morbidity did not occur in any of the study subjects.

Discussion

Summary of main findings

Our findings suggest that the extent of use of hypnotic medication is equal in patients with COPD, patients with DM and healthy controls. Approximately 22% of COPD patients did ever use a hypnotic, and when a hypnotic had been prescribed, it took an approximately equal amount of time to do so after the diagnosis was made in the three study groups. Furthermore, the types of hypnotics that were prescribed did not differ between the groups.

Strengths and limitations of the study

To our knowledge, this is the first longitudinal study that assessed the extent of use of sleep medication in primary care in patients with COPD. The longitudinal design

enabled to exclude subjects who used a hypnotic prior to the diagnosis of COPD and thus might have used the hypnotic without having COPD. The longitudinal design made it also possible to assess the time to the first prescription. If GPs were reluctant to prescribe a hypnotic to a patient with COPD, the duration to the first prescription might have been significantly longer than in the other two groups.

Furthermore, the diagnoses in this study were physician-made instead of self-reported by patients or based on, for instance, a survey questionnaire. The use of the CMR-database is an important strength of the study, because of its long term follow-up, size, completeness and trustworthiness according to the recorded morbidity.[22]

Finally, we excluded patients with known causes for secondary sleep problems and corrected our analyses for co-morbidities that are associated with increased risks for sleep problems. To assess a possible selection bias, we compared rates of sleep medication prescription after each exclusion step of figure 1 (data not shown) and found no significant differences between the patient groups after any step.

A limitation of this study is that we could not relate the use of sleep medication to the severity of the COPD, because the severity of the COPD was not documented in the database. It would have been interesting to know whether patients with more severe COPD use more hypnotics because they might experience more sleep problems, or that they use less hypnotics because GPs may be more concerned about adverse effects of the hypnotics in these patients.

Comparison with existing literature

Studies on this topic in patients with COPD are scarce. In a cross-sectional study[6] 28% of patients with COPD reported using sleep medication at that time, as compared to 10% of patients without COPD. Possible disadvantages of that study were that the diagnosis of COPD was self-reported, that potential confounders like co-morbidities were neglected and that - due to the cross-sectional design - a temporal relation could not be studied.

The differences in outcomes in our study compared to the other study may also have been caused by the different designs (longitudinal vs. cross-sectional), the use of physician-based diagnoses instead of patient-based diagnoses, and possible differences in the characteristics of our subjects in SES, gender, age and severity of the COPD (based on the same CMR-data, a previous study[23] showed a COPD severity-distribution classified according to GOLD-guidelines[24] of mild COPD 31%, moderate COPD 47%, severe COPD 19%, very severe COPD 3%).

Implications for future research or clinical practice

This study provides data on prescription of sleep medication to patients with COPD. Nearly 22% of COPD patients used sleep medication, although international guidelines advise not to prescribe these drugs in these patients. It might be that GPs

are not familiar with the possible adverse effects associated with benzodiazepines, or that GPs ignore these guidelines, perhaps because sleep problems are such a major complaint amongst patients with COPD. Future research is needed to investigate these assumptions about prescription behaviour and to improve non-pharmaceutical treatment options for sleeping problems.

Although in this study COPD patients used sleep medication as often as healthy controls and patients with DM, it can not be concluded that patients with COPD have similar rates of sleep problems as the other subjects. On the one hand, our findings may over-report (primary) sleep problems, as sleep medication may have been described for secondary sleeping problems, i.e. secondary to working in shifts or jet lags, rather than for primary sleep disturbance. On the other hand, not all episodes of sleep problems will have been treated by medication, and this will have underreported the true incidence of sleep problems. Cross-sectional studies on sleep problems in patients with COPD showed a prevalence of 14-60% in patients with COPD compared to 10-35% in controls,[3-5] and an odds ratio for sleep problems in patients with COPD of 1.6 compared to subjects without COPD,[1,2,7] but these studies may suffer from bias due to patient-reported diagnoses and co-morbidities. Well-designed studies on the prevalence of sleeping problems are needed to assess the magnitude of the problem.

In conclusion, more than 20% of patients with COPD use sleep medication, they use it as often as patients with DM or matched healthy controls, and the prescribed hypnotics did not differ between the study groups. These findings imply that GPs should pay special attention towards sleep problems and its (non-)pharmacological treatment options in patients with COPD, since the overall use of sleep medication in COPD remains substantial and these drugs may cause adverse effects in these patients.

Ethical approval

Since only information already available was used, approval of an internal review board was not needed.

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Conflicts of interests

None of the authors has any conflicts of interest to disclose.

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4

Accuracy of transcutaneous carbon dioxide measurements during cardiopulmonary exercise testing

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Abstract

Background Transcutaneous measurements of carbon dioxide ($PtcCO_2$) with current devices are proven to provide clinically acceptable agreement with arterial carbon dioxide ($PaCO_2$) measurements in several settings, but not during cardiopulmonary exercise testing (CPET).

Objectives The primary objective of this study was to investigate the agreement between $PaCO_2$ and $PtcCO_2$ measurements (using TOSCA 500 with TOSCA sensor 92) during CPET. A secondary objective was to investigate the agreement between arterial and transcutaneous oxygen saturation (SaO_2, SpO_2) as measured with this sensor during CPET.

Methods In patients with various pulmonary diseases, $PtcCO_2$ and SpO_2 were continuously measured and compared with arterial blood gas samples during CPET. A maximum bias of 0.5 kPa and 95%limits of agreement (LOA) of 1 kPa between PCO_2 measurements were determined as clinically acceptable.

Results In total 101 'paired' arterial and transcutaneous measurements were obtained from 21 patients. Bias between $PaCO_2$ and $PtcCO_2$ was -0.03 kPa with LOA from -0.78 to 0.71 kPa. Bias between SaO_2 and SpO_2 was -1.0% with LOA from –2.83 to 0.83%.

Conclusions Transcutaneous estimations of PCO_2 and SpO_2 are accurate and can be used in CPET, circumvening the need for arterial cannulation.

Keywords

Carbon dioxide, cardiopulmonary exercise testing, non-invasive monitoring, oxygen saturation, pulse oximetry, transcutaneous

Abbreviations

CPET	cardiopulmonary exercise testing
HR	heart rate
$PaCO_2$	partial pressure of carbon dioxide
PaO_2	arterial partial pressure of oxygen
$PetCO_2$	end-tidal partial pressure of carbon dioxide
$PtcCO_2$	transcutaneous partial pressure of carbon dioxide
pH	activity of hydrogen ions
r	correlation coefficient
SaO_2	arterial saturation of oxygen
SpO_2	functional saturation of oxygen

Introduction

Monitoring of gas exchange parameters is a valuable aid in interpreting the results of exercise testing. Repeated arterial blood sampling using an indwelling catheter has historically been the gold standard for monitoring carbon dioxide tensions ($PaCO_2$) and oxygen saturations (SaO_2).[1] However, this method has disadvantages like the use of costly equipment, discomfort and the association with moderate morbidity of complications.[2]

Alternatives for the measurement of PO_2, PCO_2 and SaO_2 are capillary, end-tidal and transcutaneous measurements. Capillary samples (often taken at the earlobe during exercise) and end-tidal measurements have limited accuracy.[3,4] Transcutaneous measurements have the advantage above the gold standard that they provide continuous data and that they are non-invasive and therefore less painful and safer than arterial sampling. However, studies on the accuracy and usability of various older transcutaneous sensors during exercise gave conflicting results.[4-7]

Recently, a novel transcutaneous combined sensor for PCO_2 and SaO_2 measurements (TOSCA 500 Monitoring System; Linde Medical Sensors; Basel, Switzerland) was introduced into clinical practice. Based on a Stow-Severinghaus electrode,[8] this sensor is designed for the simultaneous and continuous monitoring of PCO_2, functional oxygen saturation (SpO_2) and heart rate (HR), using a single sensor applied to the ear lobe. It does not measure PO_2.

Recent transcutaneous capnometers have been evaluated in the respiratory monitoring of newborns,[9] anaesthetized children,[10] critically ill adults,[11-13] in 'routine respiratory practice',[14] during major surgery,[13] and during sleep studies (only the SpO_2-sensor).[12] Most, but not all, studies concluded that these devices are both accurate and practicable in these settings. Reported mean difference (bias) between $PaCO_2$ and transcutaneous PCO_2 ($PtcCO_2$) ranged from -0.6 ± 1.0 kPa[13] to -0.4 ± 0.8 kPa,[9] -0.04 ± 0.7 kPa,[14] -0.03 ± 0.8 kPa,[10] 0.2 ± 0.8 kPa[11] and 0.4 ± 0.9 kPa[12] and reported correlation coefficients (r) ranged from 0.86[11] to 0.88.[12]

The use of the current transcutaneous capnometers has not yet been evaluated in cardiopulmonary exercise testing (CPET). To investigate the use of a $PtcCO_2$ sensor in CPET, we hypothesized that the $PtcCO_2$ and SpO_2 as measured by this sensor strongly correlate to the corresponding arterial measurements of $PaCO_2$ and SaO_2. The primary objective was to assess the agreement between the $PaCO_2$ and $PtcCO_2$ measurements during maximal incremental CPET. Secondary objectives were to assess the agreement between the SaO_2, the SpO_2 as measured with the sensor (SpO_2 ear) and the SpO_2 as measured with a finger pulse oximeter (SpO_2 finger) and to assess the agreement between the HR measured with the transcutaneous sensor and HR measured with electrocardiography during CPET. A tertiary objective was to assess the agreement between $PaCO_2$ and end-tidal CO_2 ($PetCO_2$) during CPET.

Methods and materials

Design, subjects and measurements

This prospective, single-centre non-interventional study was performed at the pulmonary function laboratory of a regional teaching-hospital in Arnhem, The Netherlands. The study protocol was approved by the institutional review board with a waiver of consent since the only extra burden for the subjects was the application of an ear sensor during CPET. Nevertheless, informed consent was obtained from all participants prior to study-inclusion.

Participants, who were referred from a respiratory clinic, were eligible for inclusion when they underwent a CPET including arterial sampling. The only exclusion criterion was an age below eighteen years.

A symptom limited, incremental CPET was performed using an electrically braked bicycle ergometer (Oxycon Pro, Jaeger, Hoechberg, Germany with Ergometrics 900, Ergoline, Bitz, Germany). The workload started at 0 W and increased with 10-20 W every 1-2 minutes. An arterial catheter was inserted in the a. radialis prior to the CPET and arterial blood samples for blood gas analysis (Omni S, Roche, Basel, Switzerland) were taken at rest, every three minutes after the start of the test, at the peak of exercise workload and three minutes after stopping the test. The arterial samples were immediately after sampling taken to a central laboratory and analyzed.

The $PtcCO_2$, SpO_2 and HR were continuously measured during the entire test by the ear sensor, which was set to maintain a temperature of 42°C during the entire CPET. The sensor was automatically calibrated before every CPET. It was then applied to the earlobe via an ear clip with an adhesive layer, after a drop of contact fluid was placed on the sensor. After the output of the sensor was stable (approximately ten minutes) the first arterial sample was taken and the CPET was started.

$PetCO_2$ (Oxycon Pro, Jaeger, Hoechberg, Germany) and SpO_2 (Autocorr, BCI, Red Lion, USA) were measured continuously during the entire test . Other CPET variables were monitored according to ATS/ACCP standards.[1] The occurrence of any technical problems was recorded.

Analysis

Statistical analysis for assessing agreement between variables was performed according to the method described by Bland and Altman.[15] To define the PCO_2 methods as interchangeable, we determined a maximum mean difference (bias) between $PaCO_2$ and $PtcCO_2$ or $PetCO_2$ of 0.5 kPa with 95% limits of agreement (bias $\pm$ 2 SD) of ≤1 kPa as clinically acceptable (following other authors[11,13]). To define the oxygen saturation methods as interchangeable, a bias between SaO_2 and SpO_2 ear or SpO_2 finger ≤ 2% and 95% limits of agreement ≤ 4% were determined as clinically acceptable (following previous definitions[16]).

To determine if $PtcCO_2$ (and $PetCO_2$) values significantly differed from their arterial counterparts, Student's paired t test was used. Correlation coefficients were calculated using linear regression. P-values less than 0.05 were considered significant. Data analysis was performed with statistical software (SPSS version 12.0; SPSS, Chicago, IL).

Results

Subjects

Table 1 summarizes the characteristics of the subjects (n = 21) who were enrolled in the study, and table 2 shows characteristics of their CPETs.

Table 1 Characteristics of the 21 subjects enrolled in the study

Variables	Values
Age, years	60 ± 12
Sex, M/F, n	9/12
Diagnosis	
COPD, n (%)	12 (57)
FEV_1, L	1,4 ± 0,8
FEV_1, %predicted	48,3 ± 21,1
FVC, L	2,4 ± 1,2
FEV_1 / FVC (%)	55,3 ± 10,0
Unexplained dyspnea, n (%)	3 (14)
Asthma, n (%)	2 (10)
Sarcoidosis, n (%)	1 (5)
TLCO (mmol/min/kPa)	9,64
TLCO, %predicted	84
Unexplained diffusion impairment, n (%)	1 (5)
TLCO (mmol/min/kPa)	5.07
TLCO, %predicted	63
Unexplained fatigue, n (%)	1 (5)
Lung cancer, n (%)	1 (5)
FEV_1, L	2,0
FEV_1, %predicted	63,6
FVC, L	3,9
FEV_1 / FVC (%)	51,4

Data are expressed as mean ± SD, unless stated otherwise. COPD = Chronic Obstructive Pulmonary Disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; TLCO = transfer factor of the lungs for carbon monoxide.

All subjects had a diastolic blood pressure above 60 mmHg during the entire CPET. No subjects reported the sensor to be uncomfortable, no complications occurred during the measurements and the sensor was easy to apply.

Since the subjects did not reach similar maximal workloads, the number of drawn samples varied per subject from 3 to 7, and as a consequence, a total of 101 'paired' measurements was obtained from the subjects.

Table 2 Characteristics of the CPETs of the 21 subjects

Variables	Values
Maximal work load, W	99,8 ± 50,7
Maximal work load, %predicted	85,0 ± 27,5
VO_2max, ml/min	1626 ± 760
VO_2max, %predicted	91 ± 26
Systolic blood pressure, mmHg	140 ± 37
Diastolic blood pressure, mmHg	87 ± 14
Heart rate, /min	105 ± 30

Data are expressed as mean ± SD, unless stated otherwise. VO_2max = maximal oxygen consumption.

Carbon dioxide tension

The measured $PaCO_2$ and $PtcCO_2$ values ranged from 3.28 to 7.75 kPa and 3.47 to 7.47 kPa respectively. Table 3 shows the mean ± standard deviation (SD) of measured $PaCO_2$, $PtcCO_2$ and $PetCO_2$ values, together with the related bias, precision (the SD of the bias), 95% limits of agreement and r between $PaCO_2$ and simultaneously measured $PtcCO_2$ and $PetCO_2$.

The Bland-Altman analysis of $PaCO_2$ and simultaneously measured $PtcCO_2$ revealed acceptable bias and limits of agreement and is shown in figure 1. Bias and limits of agreement of $PaCO_2$ vs. $PetCO_2$ did not meet the predefined criteria (table 3).

Figure 1 shows that the differences between $PaCO_2$ and $PtcCO_2$ values did not change when the $PaCO_2$ increased, i.e. the bias between the two methods was independent from the level of $PaCO_2$.

The average courses of the different PCO_2-measurements during the exercise tests are shown in figure 2. Student's paired t test revealed significant differences between 'paired' $PaCO_2$ and $PetCO_2$ values, but not between 'paired' $PaCO_2$ and $PtcCO_2$ values.

Table 3 Characteristics and comparison of arterial, transcutaneous and end-tidal values of PCO_2*

Type of PCO_2	n	Mean ± SD	Bias	Precision	95% Limits of agreement	r
$PaCO_2$	101	5.08 ± 0.94	NA	NA	NA	NA
$PtcCO_2$	101	5.11 ± 0.83	-0.03	0.37	-0.77 to 0.71	0.84
$PetCO_2$	101	4.03 ± 0.75	1.05	0.57	-0.09 to 2.19	0.63

* Data are expressed as kPa, unless otherwise stated and except for r. NA = not applicable; Bias = mean difference between $PaCO_2$ and this variable; n = number of samples available for analysis; Precision = SD of mean difference; 95% Limits of agreement = bias ± 2 SD; r = correlation coefficient.

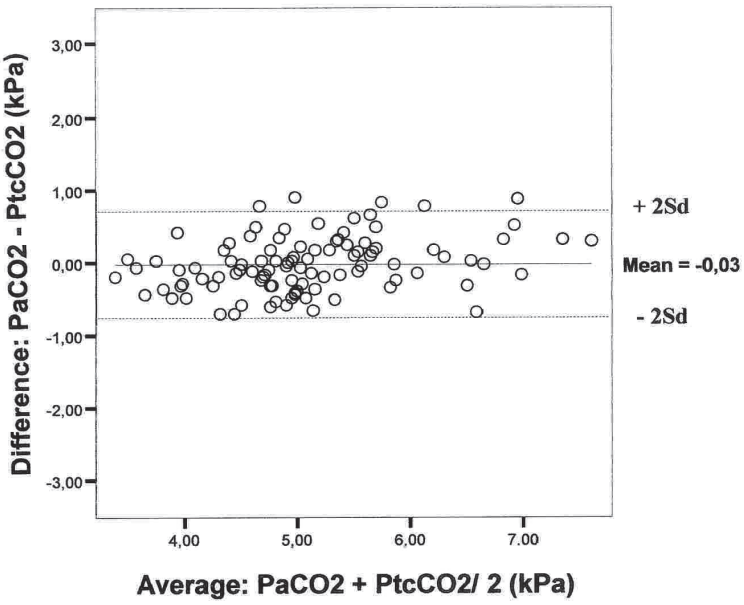

Figure 1 Bias and 95% limits of agreement between arterial and simultaneously measured transcutaneous PCO2 measurements

Dots represent absolute differences versus mean values for PCO_2 measured by arterial and transcutaneous methods. The solid line represents the mean of the differences (= bias) between $PaCO_2$ and $PtcCO_2$ (-0.03 kPa). The dashed lines are equivalent to 2 standard deviations of the mean (= 95% limits of agreement).

When looking at the individual PCO_2 measurements and trends (variation over time), no consistent under- or overestimation was observed (an overall underestimation of 0.03 kPa was found). Individual trends of $PtcCO_2$ and $PaCO_2$ corresponded well with each other (individual values and trends are not shown).

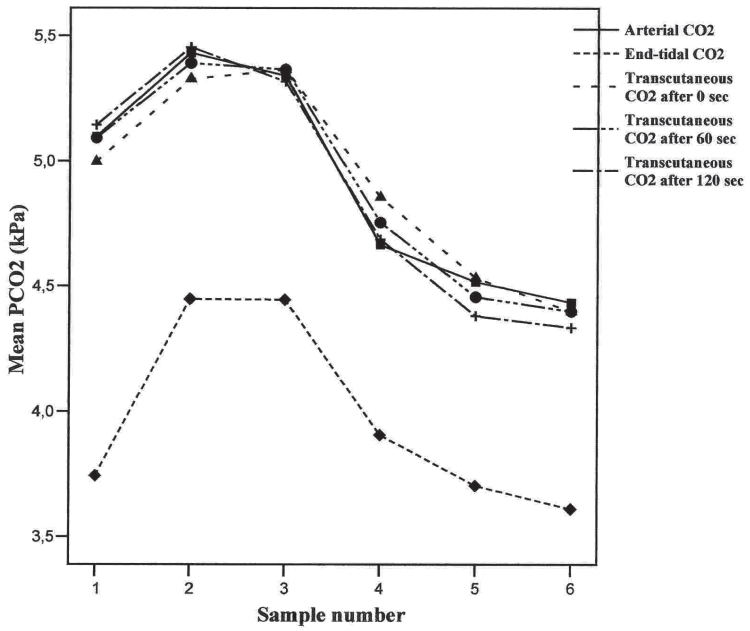

Figure 2 Average course of arterial, transcutaneous and end-tidal carbon dioxide tension (PCO_2) measurements during cardio pulmonary exercise testing (CPET)

Arterial samples were drawn right before the start of the CPET (t=0 minutes) and every 3 minutes thereafter, transcutaneous and end-tidal PCO_2 were continuously measured.

When categorized according to workload, the bias, 95% limits of agreement and r between $PaCO_2$ and $PtcCO_2$ do not show an increasing or decreasing trend when the exercise level increases (table 4).

Table 4 Comparison of arterial and transcutaneous values of PCO_2 categorised per workload*

Workload (W)	n	Bias	Precision	95% Limits of agreement	r
0-20	41	-0.02	0.38	-0.78 to 0.74	0.84
21-40	18	0.04	0.44	-0.84 to 0.92	0.84
41-60	14	-0.01	0.32	-0.65 to 0.63	0.83
61-80	4	0.03	0.62	-1.21 to 1.27	0.92
81-100	11	-0.22	0.29	-0.80 to 0.36	0.83
101-120	3	-0.07	0.27	-0.61 to 0.47	0.66
121-140	5	-0.17	0.25	-0.67 to 0.33	0.83
141-160	1	#	#	#	#
161-180	2	0.00	0.13	-0.13 to 0.13	1.00
181-200	1	#	#	#	#

* Data are expressed as kPa, unless otherwise stated and except for r; # unable to calculate this value (n = 1 in this category); Bias = mean difference between $PaCO_2$ and $PtcCO_2$; n = number of samples in this category; Precision = SD of mean difference; 95% Limits of agreement = bias ± 2 SD; r = correlation coefficient.

Oxygen saturation and heart rate

The measured SaO_2, SpO_2 ear and SpO_2 finger values ranged from 86 to 98%, 86 to 100% and 72 to 98% respectively. Table 5 shows the mean ± SD of these variables, together with the related bias, precision, 95% limits of agreement and r between SaO_2 and simultaneously measured SpO_2 ear and SpO_2 finger. The Bland-Altman analysis of SaO_2 and simultaneously measured SpO_2 ear revealed acceptable bias and limits of agreement and is shown in figure 3.

There was an acceptable bias between SaO_2 vs. SpO_2 finger, but the limits of agreement of SaO_2 vs. SpO_2 finger did not meet the predefined criteria (table 5).

The mean ± SD of heart rate values measured with electrocardiography and with the ear-sensor are shown in table 6, together with the related bias, precision, 95% limits of agreement and r.

Table 5 Characteristics of arterial and transcutaneous values of oxygen saturation*

Type of oxygen saturation	n	Mean ± SD	Bias	Precision	95% Limits of agreement	r
SaO_2	101	96.0 ± 2.5	NA	NA	NA	NA
$SpO_{2\ ear}$	101	97.0 ± 2.8	-1.00	1.83	-2.83 to 0.83	0.90
$SpO_{2\ finger}$	101	94.0 ± 3.7	1.85	2.83	-0.98 to 4.68	0.50

* Data are expressed as %, unless otherwise stated and except for r. NA = not applicable; Bias = mean difference between SaO_2 and this variable; n = number of samples; Precision = SD of mean difference; 95% Limits of agreement = bias ± 2 SD; r = correlation coefficient.

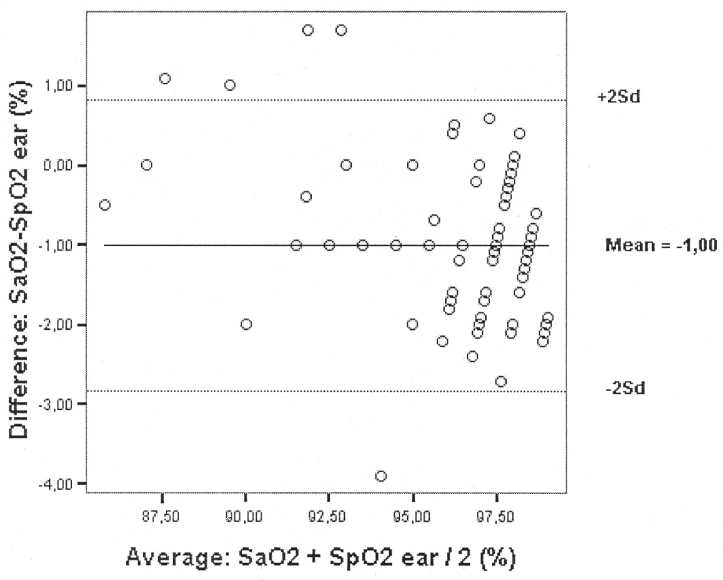

Figure 3 Bias and 95% limits of agreement between arterial and transcutaneous oxygen saturation measurements

Dots represent absolute differences versus mean values for oxygen saturation measured by arterial and transcutaneous methods. The solid line represents the mean of the differences (= bias) between SaO_2 and SpO_2 (-1.00%). The dashed lines are equivalent to 2 standard deviations of the mean (= 95% limits of agreement).

Table 6 Characteristics of heart rate measurements*

Type of measurement	Mean ± SD	Bias	Precision	95% Limits of agreement	r
ECG	105 ± 30.4	0.32 (to ear)	4.50	-4.12 to 4.82	0.99
Transcutaneous (ear)	104 ± 29.5	-0.32 (to ECG)	4.50	-4.12 to 4.82	0.99

* Data are expressed as /minute, except for r. ECG = electrocardiography; Bias = mean difference; Precision = SD of mean difference; 95% Limits of agreement = bias ± 2 SD; r = correlation coefficient.

Discussion

We studied the reliability and usability of a transcutaneous monitor to reflect PCO_2 and SpO_2 during CPET. The bias and limits of agreement between arterial and transcutaneous PCO_2 measurements were below and within the predefined criteria, and thus these data indicate that the PCO_2 assessment by this transcutaneous method during CPET in subjects with various pulmonary diseases provide clinically acceptable accuracy when compared with arterial measurements of PCO_2.

In each individual subject, the $PtcCO_2$-trend followed the $PaCO_2$-trend. Hence, when the $PaCO_2$ value increased or decreased, the $PtcCO_2$ value increased or decreased as well. Overall, the transcutaneous capnometer tends to underestimate the PCO_2 with 0.03 kPa on average with acceptable precision. This small difference is not likely to affect decisions on patient management and therefore we think one can rightfully use transcutaneously measured PCO_2 when assessing PCO_2 during ergometry.

Maybe the agreement between arterial and transcutaneous measurements would even be better when skin perfusion was improved by setting the sensor temperature higher, as other authors suggested.[12] With a better skin perfusion, a possible signal delay in transcutaneous measurements could perhaps be reduced. This issue could not be studied in the present study, since arterial values were not stable during each three minute period, due to the workloads varying every 1-2 minutes.

As the estimation of the SaO_2 with the SpO_2 sensor revealed a clinically acceptable bias, with good precision and r, the SpO_2 part of the sensor is reliable and can be used in ergometry too. And like with PCO_2, we think the small bias of 1% is not likely to influence the interpretation of oxygen saturation during exercise tests and following decisions on patient management.

One should keep in mind that the measured PCO_2 and SpO_2 values were practically within normal ranges. Our findings may therefore not apply to values outside these ranges.

Heart rate measurements with the transcutaneous device showed good agreement with those measured electrocardiographically.

The agreement of $PtcCO_2$ vs. $PaCO_2$ measurements was comparable with those found in another study,[5] which assessed $PtcCO_2$ during CPET, and better than several other studies.[9,11-13] The disparity with the latter studies could be inherent to differences in settings and subjects in those studies and it is questionable if the data of this study can justly be compared with the data of studies with critically ill adults, newborns and patients who undergo sleep studies.

In practice, advantages of the transcutaneous measurements are its easy use, its reduction of the need for arterial catheterization and capillary samples, the absence of any discomfort for patients and the provision of continuous measurements. A limitation of its use is the absence of other informative indices like bicarbonate, lactate, and PaO_2. When these indices are of interest, transcutaneous measurements can obviously not replace arterial samples. However, in selected cases, like in patients with chronic respiratory insufficiency, in patients with neuromuscular disorders, in patients undergoing repeat CPET, in patients with severe chronic obstructive pulmonary disease (COPD) and when a CPET is performed in order to assess physiological dead space or alveolar hypoventilation, transcutaneous measurements of PCO_2 and SpO_2 provide sufficient information and arterial samples can be omitted.

Another possible limitation is the dependency of the monitor on stable peripheral blood flow. Although peripheral blood flow might be unstable during a CPET, the agreement between arterial and transcutaneous measurements was still acceptable. Perhaps this agreement will be worse in patients with a lower or more unstable blood pressure than in our study population.

The shortcoming in accuracy of $PetCO_2$ measurements was not an unexpected observation, since a large proportion of our participants probably had, inherent to their diseases, ventilation/perfusion mismatches and end-tidal values represent the PCO_2 in airways, not in blood.

In conclusion, we have shown that transcutaneous assessment of PCO_2 and SpO_2, as measured with a current transcutaneous capnometer, provides clinically acceptable accuracy when compared with arterial sampling in subjects with various pulmonary diseases during exercise tests. The device is useful in interpreting exercise tests in selected cases; with an accurate and reliable transcutaneous PCO_2 and SpO_2 sensor in combination with the measurement of expired gases and minute ventilation, indices of cardio respiratory quality can be assessed and arterial cannulation can be avoided.

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Conflict of interest statement

All authors declare that they have no financial involvement in any organization discussed in this manuscript nor any other potential conflicts of interest.

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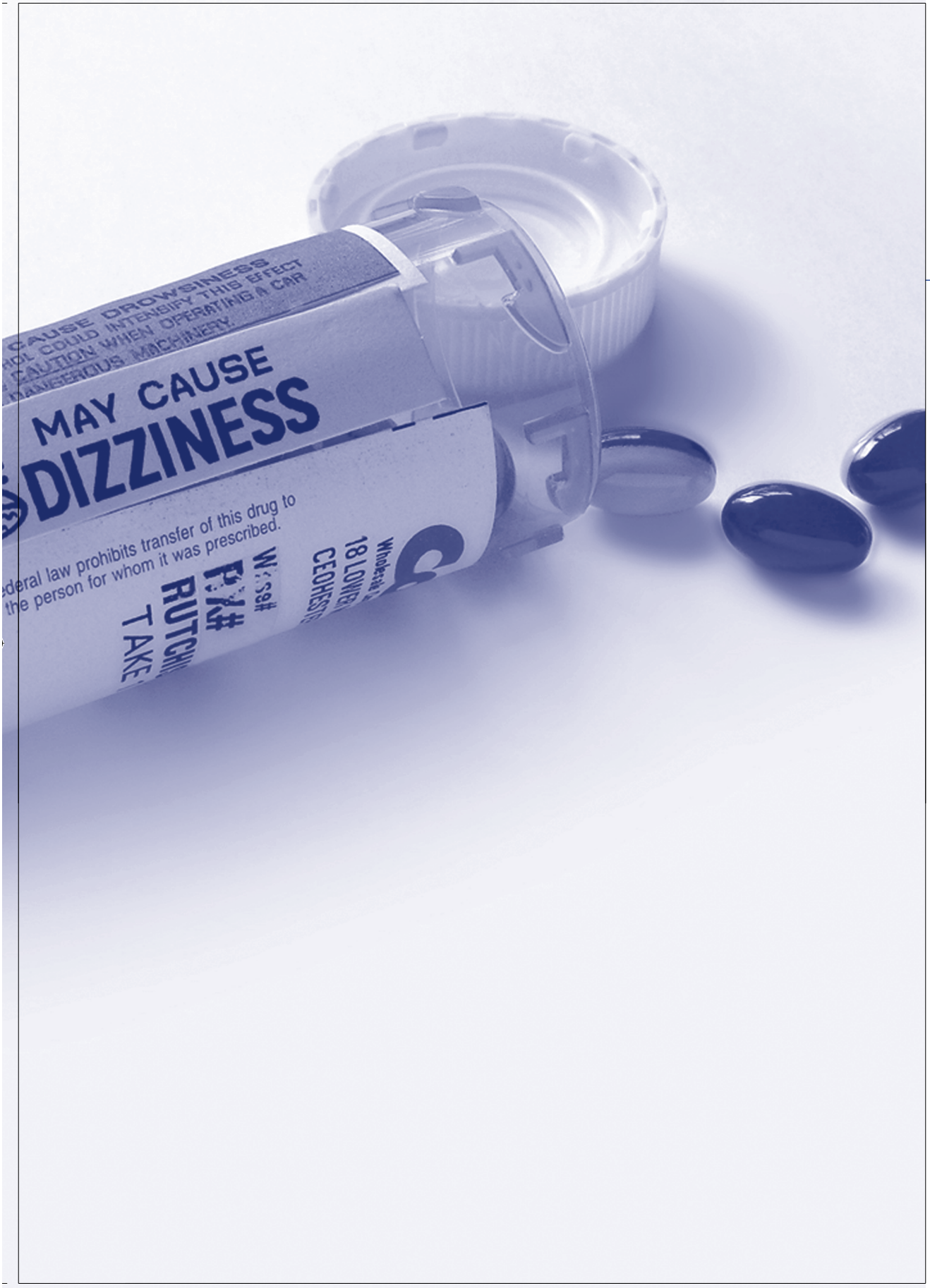
CAUSE DROWSINESS
HOL COULD INTENSIFY THIS EFFECT
CAUTION WHEN OPERATING A CAR
DANGEROUS MACHINERY.
MAY CAUSE
DIZZINESS
ederal law prohibits transfer of this drug to
the person for whom it was prescribed.

5

Temazepam 10 mg does not affect breathing and gas exchange in patients with severe normocapnic COPD

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Abstract

Background Benzodiazepines can improve sleep quality, but are also thought to cause respiratory depression in patients with chronic obstructive pulmonary disease (COPD). The aims of this study were to assess the effects of temazepam on indices of circadian respiratory function, dyspnea, sleep quality, and sleepiness in patients with severe COPD and insomnia.

Methods In a double-blind, randomized, placebo-controlled, cross-over study in 14 stable patients with COPD (mean FEV_1 0.99 ± 0.3 L) with insomnia, polysomnography with continuous transcutaneous capnography and oximetry, arterial gas sampling, hypercapnic ventilatory response, multiple sleep latency test, Epworth Sleepiness Scale, dyspnea and sleep visual analogue scales (VAS) were performed at baseline, after one week of temazepam 10 mg at bedtime and after one week of placebo.

Results Temazepam did not cause statistically significant changes in mean transcutaneous carbon dioxide tension during sleep compared to placebo (5.9 ± 1.0 kPa vs. 6.3 ± 1.4 kPa, p-value 0.27), nor in mean oxygen saturation (92 ± 3% vs. 92 ± 2%, p-value 0.31), nor in any of the other investigated variables, except for the total sleep time and sleep latency VAS, which improved with temazepam.

Conclusions One week usage of temazepam 10 mg does not influence circadian respiratory function, dyspnea, and sleepiness in patients with stable, severe, normocapnic COPD and insomnia and it improves total sleep time and subjective sleep latency. However, this is a preliminary explorative study for assessing the feasibility to perform a larger study on this topic. The clinical implications of this study are very limited.

This study was registered at www.ClinicalTrials.gov as 'Effects of temazepam in patients with chronic pulmonary obstructive disease' (ID number NCT00245661).

Keywords

Benzodiazepines, Chronic Obstructive Pulmonary Disease, gas exchange, insomnia, sleep, temazepam

Abbreviations

ABG	arterial blood gas
AHI	apnea-hypopnea-index
COPD	chronic obstructive pulmonary disease
HCVR	hypercapnic ventilatory response
HR	heart rate
ODI	oxygen desaturation index
$PaCO_2$	arterial partial pressure of carbon dioxide
PaO_2	arterial partial pressure of oxygen
$PetCO_2$	end-tidal partial pressure of carbon dioxide
$PtcCO_2$	transcutaneous partial pressure of carbon dioxide
PSG	polysomnography
REM	rapid eye movements
SaO_2	arterial saturation of oxygen
SpO_2	functional saturation of oxygen
TST	total sleep time
VAS	visual analogue scale

Introduction

The sleep of patients with chronic obstructive pulmonary disease (COPD) is often of poor quality.[1-5] Up to fifty-three percent of these patients report sleep-related complaints[2] characterized by a longer sleep latency, more frequent arousals and awakenings, and more daytime sleepiness than healthy individuals.

Sleep disturbances can substantially reduce patients' quality of life[6] and, as a result, patients often consult their physician for hypnotics. Twenty-eight percent report frequent use of hypnotics compared to 10% in age-matched controls.[4] Polysomnographic recordings show reductions in total sleep time (TST) and duration of slow wave and rapid eye movement (REM) sleep, more sleep state changes, and an increase in number and severity of arousals during sleep.[5] Benzodiazepines are proven to influence sleep quality beneficially[7] and are the first-choice hypnotics nowadays.[8,9]

However, ATS/ERS-guidelines[10] state that hypnotics should be avoided in patients with severe COPD. Benzodiazepines may negatively affect breathing during sleep in these patients in several ways;[11-14] they may decrease the central sensitivity to hypoxic and hypercapnic stimuli,[11] they decrease the arousal response following hypoxemia or hypercapnia,[12] and they increase upper airway resistance, mainly due to myorelaxation.[13] Other studies, by contrast, did not show any adverse effects of benzodiazepines in patients with COPD.[15-18]

Several problems occur when interpreting and comparing these studies due to methodological flaws like a single night of drug usage (a possible carry-over effect may be overlooked), inclusion of subjects with varying severity of COPD, the use of different benzodiazepines, and the use of different respiratory outcome variables. Furthermore, none of these studies were performed in COPD patients with insomnia, precisely the patients one might prescribe a hypnotic to. So although several studies have been published hypnotic about both the benefits and the risks of the use of benzodiazepines in patients with COPD, their use still remains controversial. The effects of temazepam on breathing have, to our knowledge, not been studied in patients with COPD.

The primary objective of this study was therefore to examine whether prolonged usage of the benzodiazepine temazepam influences indices of breathing and gas exchange during sleep in patients with severe COPD who experience insomnia. Secondary objectives were to assess the effects of prolonged usage of temazepam on diurnal breathing, gas exchange, and dyspnea in patients with severe COPD and insomnia. In addition, sleep quality and diurnal sleepiness were examined in these patients.

Methods and materials

Subjects

Subjects were recruited at the outpatient centre of the Respiratory Medicine Department of the Rijnstate Hospital, Arnhem, the Netherlands. Patients were eligible for inclusion if they had COPD GOLD stage 3 or 4[19] without an exacerbation in the past 6 weeks, and if they experienced insomnia. GOLD stages 3 or 4 were chosen because these patients were anticipated to show the most profound adverse effects when these would occur. Exclusion criteria were the use of any medication influencing sleep architecture within 4 weeks before inclusion, a history of alcohol, benzodiazepine or other drug dependence, allergy to a benzodiazepine, a clinically relevant sleep apnea syndrome (defined as having a apnea-hypopnea-index (AHI) ≥ 15, either measured before enrolment or at the baseline polysomnography (PSG)), and dependency on long-term oxygen therapy. Written and oral informed consent was obtained from all participants and the study was approved by our Institutional Review Board.

Study design

All subjects were studied for three weeks in a double-blind, randomized, cross-over design. Subjects were randomized after the baseline measurements to use 10 mg temazepam or placebo once a day orally, both during one week, separated by a washout-period of one week. Randomization was done by the hospital pharmacy. Subjects were instructed to take the study medication 30 minutes before they went to bed. Temazepam was proven to improve sleep quality previously.[20]

The rationale for selecting the benzodiazepine temazepam was based on its efficacy,[20] its frequent use as a hypnotic and Dutch guidelines,[21] which advise the use of temazepam 10 mg (or nitrazepam) as first choice hypnotic due to its intermediate half-life and minimal daytime side effects.[8,9]

The temazepam and placebo were provided by the hospital pharmacy as a solution, which was produced as previously described.[22]

Measurements

Before enrolment, all subjects underwent pulmonary function testing with reversibility (after 400 μg salbutamol). A baseline polysomnography (PSG) and a multiple sleep latency test (MSLT) were done for acclimatization purposes and to screen for any possible sleeping disorders. At days 7 and 21 all subjects participated in the following measurements: an arterial blood gas (ABG) was taken at rest, the ventilatory response to hypercapnia (HCVR) was measured, in normoxic conditions, by the steady state method,[23] an MSLT[24] consisting of 4 naps at 2-hour intervals was performed, subjective dyspnea, sleepiness, sleep latency and sleep quality in the past week

were assessed with 10-point visual analogue scales (VAS) and the Epworth Sleepiness Scale (ESS) was used to evaluate subjective sleepiness after temazepam and placebo use.[25] Higher ESS scores indicate a greater sleepiness, and a cut-off point of 10 is often used to distinguish between normal (<10) and excessive (≥10) daytime sleepiness.[25]

To assess sleep quality with temazepam and placebo, a PSG was performed at night 7 and night 21, which included continuous electro-oculography (EOG), submental muscle electromyography (EMG) and electro-encephalography (EEG) (Sleepscreen, Viasys Healthcare, Hoechberg, Germany). Together with the PSG, heart rate and rhythm were measured by a continuous electrocardiography and oxygen saturation (SpO_2) and transcutaneous carbon dioxide ($PtcCO_2$) were continuously measured (TOSCA 500, Linde Medical Sensors, Basel, Switzerland) to assess gas exchange during sleep. Furthermore, airflow- and respiratory effort were measured with a nasal/oral thermistor and thoracic and abdominal piezoelectric belts. A bilateral anterior tibialis EMG was performed to exclude periodic leg movements.

Definitions

An apnea was defined as a cessation of oronasal airflow lasting ≥ 10 seconds, a hypopnea was defined as a decrease in airflow and/or chest wall movement of 50% or more occurring simultaneously with an oxygen desaturation, the AHI was defined as the number of apneas and hypopneas per hour sleep, an oxygen desaturation was defined as a reduction in oxygen saturation of ≥ 4% from baseline and the oxygen desaturation index (ODI) was defined as the number of oxygen desaturations per hour sleep.

Parameters to describe sleep quality were the total sleep time (TST), sleep-onset latency (SOL), sleep efficiency (SE), the number of arousals, and the amount of REM and non-REM (nREM) sleep.

Analysis

We aimed to detect a 0.5 kPa difference in $PtcCO_2$ (based on previous studies)[26,27] at the 5% significance level for a one-sided test with 80% power. With a crossover design, this would require 14 patients. To anticipate possible dropouts, we planned to include 17 patients.

The primary outcome parameters were the $PtcCO_2$ and SpO_2 levels during sleep, and secondary parameters were the AHI and DI, the HCVR, the ABG values, the levels of subjective and objective sleepiness (represented by VAS-scales, ESS and MSLT outcomes), dyspnea sensation (VAS), sleep latency (VAS), sleep quality (VAS), and the sleep quality as measured by PSG. Both the slope (minute ventilation (VE) / end-tidal carbon dioxide tension ($PetCO_2$)) and intercept (L/min) of the HCVR were analyzed.

Sleep was manually staged according to standard methods[28] by two qualified sleep technicians blinded to the subject's treatment status.

Data are expressed as means (SD) for quantitative variables or as means ± SEM when percentages are compared. We used a Student's t test for paired series and ^{2} – test for continuous and discrete variables respectively to compare between the data obtained after a week temazepam and the data obtained after a week placebo. P values < 0.05 were considered statistically significant. All statistical analyses were carried out using the SPSS version 12.0 statistical package (SPSS, Inc., Chicago, IL).

Results

Subjects

Fig. 1 shows a flow diagram of the selection of the subjects. Seventeen patients were enrolled in the study, but 3 subsequently dropped out. One subject appeared from the first PSG to have an obstructive sleep apnea-hypopnea syndrome and was therefore excluded; another subject developed an exacerbation of his COPD during the study and was excluded, and a third subject withdrew from participation due to the burden of the measurements.

Fourteen subjects completed the study-protocol; their demographic data and characteristics are presented in Table 1. The sleep-related complaints of the subjects were difficulty maintaining sleep (experienced by 8 subjects), a prolonged sleep-onset latency (experienced by 7 subjects), extensive daytime sleepiness (experienced by 6 subjects), and nocturnal dyspnea (experienced by 2 subjects).

Respiratory and sleep variables

The effects of temazepam and placebo on diurnal and nocturnal respiratory variables are listed in Table 2; their effects on variables concerning sleep architecture and sleep quality are listed in Table 3 and their effects on daytime sleepiness are listed in Table 4.

None of the changes were statistically significant, except for the TST (increased), the amount of stage 2 sleep (increased), and the VAS-scale on sleep latency (improved).

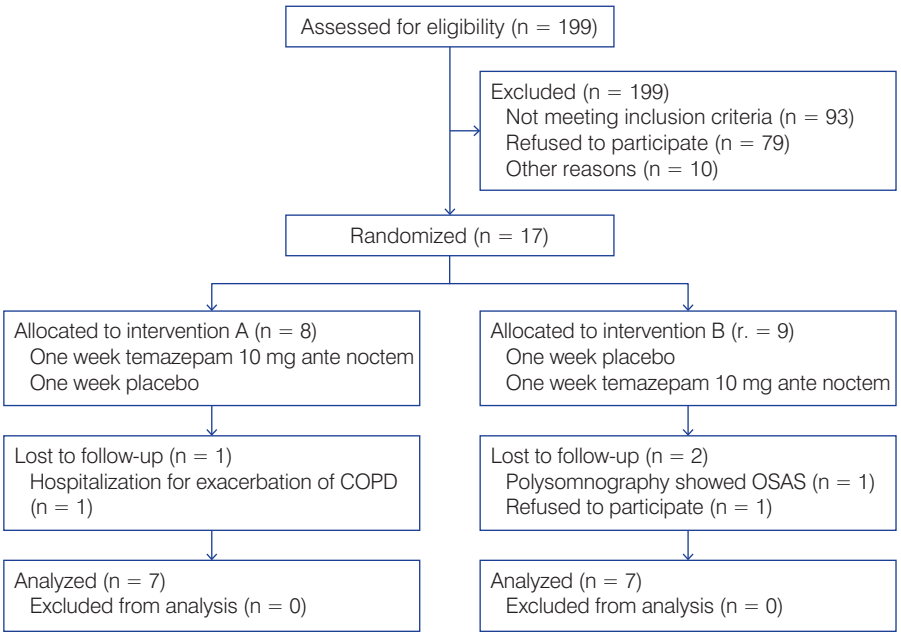

Figure 1 Flow diagram of selection of subjects

Table 1 Characteristics of the 14 subjects enrolled in the study*

Patient data	Values
Age, yr	61.6 ± 8.0
Sex (M/F)	10/4
FEV_1, L	0.99 ± 0.3
FEV_1, % predicted	33.5 ± 9.2
FEV_1 / FVC (%)	32.7 ± 13
Reversibility of FEV_1, % predicted	3.34 ± 3.6
BMI, kg/m^2	23.2 ± 5
Baseline $PaCO_2$, kPa	5.4 ± 0.4
Baseline PaO_2, kPa	9.6 ± 0.7
Smoking status, pack-years Former, n Current, n	43.1 ± 15.9 10 (71) 4 (29)

Data are expressed as mean ± SD or No. (%). BMI=Body Mass Index; FEV_1=Forced Expiratory Volume in 1 second; FVC=Forced Vital Capacity; $PaCO_2$= arterial pressure of carbon dioxide; PaO_2= arterial pressure of oxygen.

Table 2 Respiratory variables*

Variables	Baseline	Temazepam	Placebo	pValue†
$PtcCO_2$ during sleep, kPa				
Mean	6.2 ± 0.6	5.9 ± 1.0	6.3 ± 1.4	0.27
Highest	6.9 ± 0.6	6.4 ± 1.1	7.3 ± 2.0	0.13
Lowest	5.3 ± 0.7	4.9 ± 1.2	5.5 ± 1.0	0.08
% TST with $PtcCO_2$ > 6 kPa	9.9 ± 22.1	7.8 ± 26.5	8.0 ± 26.5	0.75
SaO_2 during sleep, %				
Mean	92 ± 2	92 ± 3	92 ± 2	0.31
Lowest	82 ± 5	81 ± 4	83 ± 5	0.24
% TST with SaO_2 <90%	8.3 ± 19.3	7.2 ± 11.0	6.1 ± 16.4	0.96
AHI, /hr TST	5.4 ± 5.9	6.8 ± 6.3	5.1 ± 5.2	0.40
ODI, /hr sleep	10.1 ± 8.8	8.9 ± 8.6	7.9 ± 6.3	0.61
HCVR				
Slope (L/min/kPa)	4.0 ± 4.4	5.6 ± 4.5	5.7 ± 4.8	0.99
Intercept (kPa)	-6.7 ± 23.4	-13.7 ± 20.7	-13.4 ± 21.5	0.96
Daytime $PaCO_2$, kPa	5.4 ± 0.4	5.5 ± 0.6	5.5 ± 0.5	0.62

Table 2 Continued

Variables	Baseline	Temazepam	Placebo	pValue†
Daytime PaO_2, kPa	9.6 ± 0.7	9.3 ± 1.0	9.6 ± 0.9	0.14
Subjective dyspnea (VAS), pts	3.8 ± 2.6	4.2 ± 2.9	4.1 ± 2.5	0.90

Data are expressed as mean ± SD; †for comparisons between temazepam and placebo; AHI=apnea-hypopnea-index; HCVR=ventilatory response to hypercapnia; ODI=desaturation index; $PetCO_2$= end-tidal partial pressure of carbon dioxide; $PtcCO_2$=transcutaneous partial pressure of carbon dioxide; SaO_2= oxygen saturation; TST=total sleep time; VAS=visual analogue scale; ΔV_E=change in minute ventilation.

Table 3 Sleep quality and architecture variables*

Variables		Baseline	Temazepam	Placebo	pValue†
TST, hr.		5.7 ± 1.2	6.3 ± 1.0	5.4 ± 1.1	0.03
SE, %		81.0 ± 10.7	86.3 ± 10.1	80.8 ± 14.1	0.19
SOL, min.		43.2 ± 38.7	21.1 ± 20.8	21.6 ± 11.7	0.94
Arousal index, no./hr TST		6.0 ± 3.2	6.3 ± 4.3	5.4 ± 1.8	0.49
REM sleep latency, min.		137.9 ± 82.6	114.1 ± 58.9	142.4 ± 74.3	0.22
nREM 1,	% of TST	27.0 ± 13.4	21.8 ± 8.8	25.1 ± 13.9	0.45
	minutes	98.1 ± 57.2	88.4 ± 37.7	75.1 ± 45.8	0.38
nREM 2,	% of TST	37.5 ± 11.8	45.6 ± 7.7	42.9 ± 11.1	0.50
	minutes	130.8 ± 54.5	168.8 ± 34.4	140.0 ± 44.6	0.03
SWS,	% of TST	21.0 ± 10.3	19.4 ± 7.9	19.3 ± 7.6	0.93
	minutes	68.8 ± 28.7	74.9 ± 35.8	61.1 ± 23.0	0.10
REM,	% of TST	14.4 ± 6.9	13.2 ± 8.0	12.8 ± 7.0	0.84
	minutes	48.3 ± 22.6	51.0 ± 32.3	49.7 ± 42.7	0.93
nREM / REM, %		18 ± 9	16 ± 11	15 ± 10	0.76
Sleep latency (VAS), pts		4.4 ± 3.2	3.3 ± 2.8	4.6 ± 3.2	0.03
Sleep quality (VAS), pts		4.3 ± 3.0	3.4 ± 3.0	4.3 ± 3.6	0.11

*Data are expressed as mean ± SD; †for comparisons between temazepam and placebo; nREM=non-rapid eye movement sleep; REM=rapid eye movement sleep; SE=sleep efficiency; SOL=sleep-onset latency; SWS=slow wave sleep (i.e. sleep stages nREM 3 and 4); TST=total sleep time; VAS=visual analogue scale.

Table 4 Variables on objective and subjective diurnal sleepiness*

Variables	Baseline	Temazepam	Placebo	pValue†
MSLT, min.	16.5 ± 4.6	15.8 ± 4.6	14.7 ± 4.6	0.38
ESS, pts.	6 ± 4	5 ± 4	6 ± 4	0.13
Daytime sleepiness (VAS), pts	4.7 ± 3.0	4.7 ± 3.2	4.8 ± 2.6	0.86

*Data are expressed as means ± SD; † for comparisons between temazepam and placebo; ESS=Epworth Sleepiness Scale; MSLT=multiple sleep latency test; VAS=Visual Analogue Scale.

Discussion

The main finding of the present study is that prolonged usage of temazepam 10 mg in the evening did not influence indices of gas exchange and breathing during sleep in our patients with severe normocapnic COPD who experience insomnia. Furthermore, it seems that diurnal gas exchange, respiratory centre control, subjective dyspnea, objective and subjective daytime sleepiness were not affected by temazepam compared to placebo, while TST and subjective sleep latency improved in these patients.

Neither the indices of gas exchange during sleep ($PtcCO_2$ and SpO_2), nor the indices of breathing during sleep (AHI and ODI) were affected by temazepam compared to placebo. Evidence that diurnal gas exchange, respiratory centre control, and subjective dyspnea are not affected by temazepam is that daytime $PaCO_2$, PaO_2, HCVR, and VAS scales remained unchanged with temazepam.

Our findings are consistent with those of prior reports,[15-18] but contrary to those found in other studies.[11,14] These studies were all randomized clinical trials with a sample size ranging from 9 to 24 subjects. One study[11] had a study population of healthy subjects, the other five only included patients with COPD ($FEV_{1\ predicted}$ ranging from 17 to 76%). The study drugs were diazepam,[11,18] flunitrazepam,[14,15] nitrazepam,[15] triazolam,[14,17] zolpidem,[14,16] and zopiclone.[11] The adverse outcomes encountered were a reduction of the hypercapnic ventilatory response caused by diazepam,[11] and increases in $PaCO_2$ and decreases in minute ventilation caused by flunitrazepam and triazolam.[14]

The differences in outcomes might be explained by one of the following reasons. First, outcomes are likely to be influenced by the pharmacological profiles of the used benzodiazepines. This is, to our knowledge, the first study to evaluate temazepam in the present context. Comparisons to other studies should therefore be done with care. The intermediate half-life of temazepam may play a role in the absence of diurnal effects, but this can only be seen as an advantage of the drug.

Second, our outcomes might have been different when a higher dose of temazepam would have been used. Although larger doses (15-20 mg temazepam) are sometimes prescribed for insomnia, we chose to use the smallest dose likely to be effective. Further studies are needed to assess the adverse effects of larger doses.

Third, the designs of studies and duration of drug use (a single night vs. one week) might play a role in outcomes. With the prolonged use as was done in this study, a possible carry-over effect could be examined. Fourth, it might be that our study was too under-powered to demonstrate an effect. This might especially concern any secondary variables, since the present sample size was based on the primary variables $PtcCO_2$ and SpO_2. Outcomes in secondary variables might have been different with a larger sample size. Due to the crossover design, this study was capable to detect a 0.5 kPa difference in $PtcCO_2$ and a 4% difference in nocturnal SpO_2, both with 80% power, with only 14 subjects.

Temazepam beneficially influenced the sleep quality by lengthening the TST, it improved the subjective sleep latency, and increased the amount of stage 2 nREM sleep. It did not significantly influence other parameters of sleep quality and sleep architecture nor did it improve objective and subjective daytime sleepiness in our population.

A strong point of this study is the measurement of $PtcCO_2$ during sleep. To our knowledge, this is one of the first studies where $PtcCO_2$ was measured to assess the effects of a benzodiazepine on gas exchange during sleep. Nocturnal measurements of $PtcCO_2$ have rarely been performed due to the insufficient accuracy and risk of burns associated with older capnometers. The current transcutaneous device, by contrast, has been reported to accurately assess PCO_2 in routine respiratory practice,[29] in critically ill adults,[30] in newborns,[31] and during cardiopulmonary exercise testing[32] without the occurrence of any major complications. Although this apparatus has not yet been validated during sleep, we think that it can accurately measure nocturnal $PtcCO_2$ since its use on an intensive care unit is also for an extended period of time.

Other strong points are the inclusion of subjects with only severe COPD ($FEV_{1\ predicted}$ $<$50%), who in addition experienced insomnia, the study period of 7 days instead of a single day or night, and the timing of the measurements; unlike several previous studies, we not only examined the subjects awake, but also while they were asleep.

Limitations of this study are present as well. We did not compare temazepam to other benzodiazepines or a non-benzodiazepine benzodiazepine-receptor agonist (NBBRA). An intermediate-acting benzodiazepine was chosen since long- and short-acting benzodiazepines are not recommended for the short-term management of insomnia, and because only minor differences in efficacy exist between NBBRAs and benzodiazepines,[33] these two groups of hypnotics were not compared with each other.

Another limitation is the relatively low dosage of temazepam, used for reasons mentioned above. Furthermore, at the start of the second study week the stability of the COPD was not objectively confirmed with spirometry, but only assessed on clinical grounds.

Temazepam caused no adverse respiratory events for the group as a whole, but it is possible that these events occur on a individual scale, because some individuals, like patients with other, unfavourable pharmacodynamics, patients who may take extra doses of temazepam, or patients with other sleep disturbances, might be more susceptible to adverse events than others. Therefore, the sample size may have been too small to include some of those 'more susceptible' patients. Studies with larger sample sizes will be needed to include some of those more susceptible patients as well.

Our conclusions cannot safely be applied to other, related situations such as the use of other benzodiazepines, larger doses of temazepam, periods longer than our study period of one week, or to patients with an exacerbation of their COPD, to hypercapnic COPD patients, to patients with COPD plus an sleep-apnea syndrome or to patients with other pulmonary diseases. In the mentioned situations and patients groups, use of temazepam is still to be seen as experimental.

In the light of the mentioned limitations, this study is best to be seen as a preliminary explorative study for assessing the feasibility to perform a larger study on this topic, and the clinical implications of this study are very limited. Larger studies would be necessary to determine the role of benzodiazepines and NBBRAs in the pharmacological management of insomnia during an exacerbation in patients with (severe) COPD and in the aforementioned situations and patients groups. Until those studies are performed, guidelines on this subject like the ATS-ERS guideline[10] should not be more liberate and temazepam and other benzodiazepines should still be used with great caution in these situations and patients. Also, temazepam should only be used in patients with COPD when other, non-pharmacological therapies for insomnia have failed, and then only for a short period. Its use should carefully be watched and re-evaluated when the patient develops an exacerbation of the COPD or worsens for other reasons.

Physicians should be aware that the prevalence of insomnia in patients with COPD can be as high as 50%,[2] and that insomnia can have a major negative impact on the quality of life of these patients. Hence, by improving sleep quality physicians have a tool to presumably improve the quality of life of their patients with COPD.

In conclusion, in this preliminary study repeated doses of temazepam did not adversely affect nocturnal respiratory function in our severe but stable normocapnic COPD patients without complications, but it did improve TST and sleep-onset latency. Furthermore, temazepam did not affect diurnal gas exchange, diurnal central respiratory centres, and subjective dyspnea.

Temazepam can, in our view, not automatically be dismissed from patients with stable, normocapnic COPD who experience insomnia and consequently have a reduced quality of life, but it remains to be seen as a last resort when other, non-pharmacological remedies have failed.

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Conflict of Interest Statement

None of the authors has potential conflicts of interest.

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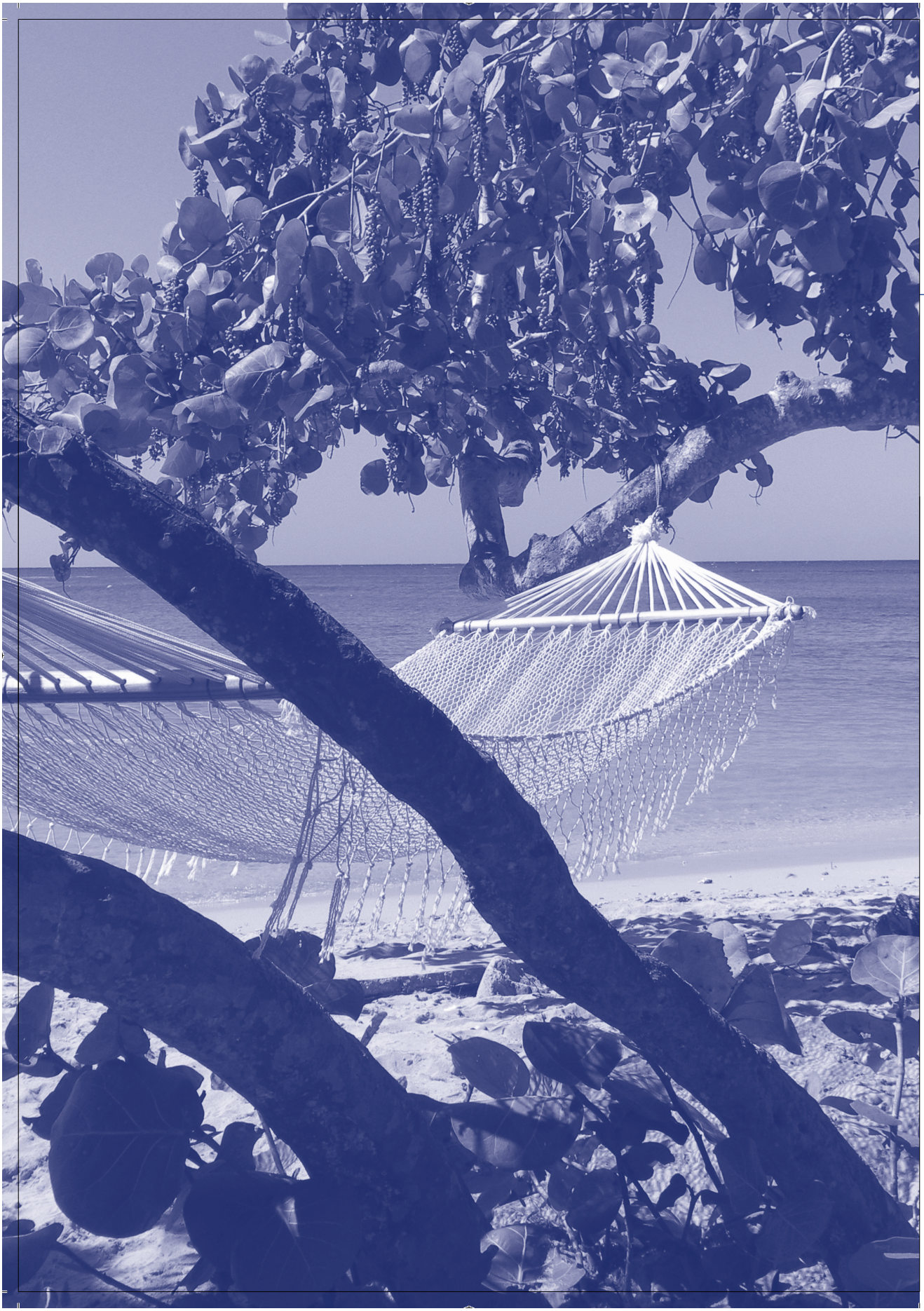

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Manual vs. automated analysis of polysomnographic recordings in patients with chronic obstructive pulmonary disease

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Abstract

Purpose The sleep quality, as assessed by polysomnography (PSG), of patients with Chronic Obstructive Pulmonary Disease (COPD) can severely be disturbed. The manual analysis of PSGs is time-consuming and computer systems have been developed to automatically analyse PSGs. Studies on the reliability of automated analyses in healthy subjects show varying results, and the purpose of this study was to assess whether automated analysis of PSG by one certain automatic system in patients with COPD provide accurate outcomes when compared to manual analysis.
Methods In a retrospective study the full-night polysomnographic recordings of patients with and without COPD were analysed automatically by Matrix Sleep Analysis software and manually. The outcomes of manual and automated analyses in both groups were compared using Bland-Altman plots and Students' paired t tests.
Results 50 PSGs from patients with COPD and 57 PSGs from patients without COPD were included. In both study groups agreement between manual and automated analysis was poor in nearly all sleep and respiratory parameters, like total sleep time, sleep efficiency, sleep latency, amount of REM sleep and other sleep stages, no. of arousals, apnea-hypopnea-index and oxygen desaturation index.
Conclusion Automated analysis of PSGs by the studied automated system in patients with COPD have poor agreement with manual analysis when looking at sleep and respiratory parameters and should therefore not replace the manual analysis of PSG recordings in patients with COPD.

Key words

Computerized scoring, polysomnography, chronic obstructive pulmonary disease, sleep stage scoring

Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnea-Hypopnea Index
COPD	Chronic obstructive pulmonary disease
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
FEV_1	Forced Expiratory Volume in one second
nREM	non-REM sleep
ODI	Oxygen desaturation index
OSAHS	Obstructive Sleep Apnea-Hypopnea Syndrome
PLM	Periodic Leg Movements
PSG	Polysomnography
REM	Rapid Eye Movement
SE	Sleep Efficiency
SOL	Sleep-onset Latency
SpO_2	Oxygen saturation
TST	Total Sleep Time

Introduction

Patients with chronic obstructive pulmonary disease (COPD) experience higher rates of sleep problems, characterized by a longer sleep latency, more frequent arousals and awakenings, and more daytime sleepiness than healthy individuals.[1] Also, their sleep quality is often disturbed.[2-5] Sleep problems are ranked third, after dyspnea and fatigue, in frequency of complaints of patients with COPD.[6]

Sleep quality can objectively be evaluated by a polysomnography (PSG), which consists of continuous electrooculography (EOG), submental muscle electromyography (EMG) and electroencephalography (EEG) during sleep. Together with the PSG, heart rate and rhythm, oxygen saturation (SpO_2), airflow, respiratory effort and bilateral anterior tibialis EMG are usually measured to assess cardiac disturbances, respiratory problems and periodic leg movements (PLM) during sleep.

The manual analysis of a PSG is considered the gold standard for evaluating PSGs.[7] However, manual analysis is time-consuming and costly since each epoch (usually a period of 30 seconds of data) has to be evaluated individually and a PSG normally consists of up to 1000 epochs.

In the past decade, several computer systems have been developed to analyse PSG recordings automatically,[8-19] and varying agreement rates were reported. These studies have only been performed in healthy subjects,[8-12] in patients with sleep-apneas,[13-15] in elderly,[16] in depressed and insomniac patients,[17] and in children,[18] but never in patients with COPD.

The Digital Task Force of the American Academy of Sleep Medicine (AASM), evaluating the quality of these automated analyses, concluded with several remarks that human and computer agreement with some systems had reached the level comparable with the level of human scoring agreement between different laboratories.[20] Furthermore, they conclude that 'accuracy must be evaluated in both normal samples and appropriate pathophysiological samples of recordings.'

Therefore, the objective of this study was to assess the agreement between the automated analysis by the analysis software currently available in our institution and the manual analysis of sleep and respiratory variables of PSGs in patients with and without COPD.

Methods

This was a retrospective study based on data recorded between April 2006 and December 2007 at the sleep laboratory of the Rijnstate Hospital in Arnhem, The Netherlands.

Subjects

The study population consisted of patients seen at the outpatient clinic of our pulmonary department. As part of standard practice, all patients performed a chest X-ray, pulmonary function tests, and an Epworth Sleepiness Scale prior to the PSG. All COPD patients who had undergone a PSG in the before mentioned period were included. The control group consisted of patients without COPD (confirmed by spirometry) who had performed a PSG at the same sleep laboratory in the same period as the COPD group. Exclusion criteria were the absence of sufficient PSG data and the absence of spirometric data.

Polysomnography

Full night PSG studies were performed which included continuous EOG, submental muscle EMG and EEG, placed according to the international 10-20 system (Sleepscreen, Viasys Healthcare, Hoechberg, Germany). Simultaneously with the PSG the following data were continuously recorded: an electrocardiogram, oxygen saturation (SpO_2), airflow (nasal-oral thermistor), respiratory effort (thoracic and abdominal piezoelectric belts), body position, and bilateral anterior tibialis EMG (to measure periodic leg movements). All data were recorded and autoscored by Matrix Sleep Analysis software (Viasys Healthcare, Hoechberg, Germany). Details on the performance and tuning of the software were not provided by the manufacturer.

Manual analysis of the PSG data was done by two experienced technicians. Each technician analyzed the sleep and respiratory variables of half of the patients and the control group. The variables are shown in Table 2 and 3. They staged sleep according to standard criteria of Rechtschaffen and Kales on 30-second epochs.[21] The predominant sleep stage was scored for each epoch. At the time the data were gathered and analysed, the new AASM scoring rules were not yet common practice at our institution.

Definitions

COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)-guideline.[22] Parameters to describe sleep quality were the total sleep time (TST), REM sleep latency, sleep efficiency (SE), the number of arousals, and the amount of REM and non-REM (nREM) sleep stages, as defined by the AASM[7] and the sleep-onset latency (SOL), defined as the time to the first epoch to any sleep. Arousals from sleep were also defined according to AASM guidelines,[7] and the

arousal index was defined as the number of arousals per hour sleep. An apnea was defined as a cessation of oronasal airflow lasting ≥ 10 seconds, a hypopnea was defined as a decrease in airflow and/or chest wall movement of 50% or more occurring simultaneously with an oxygen desaturation, the apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour sleep, an oxygen desaturation was defined as a reduction in oxygen saturation of ≥ 4% from baseline and the oxygen desaturation index (ODI) was defined as the number of oxygen desaturations per hour sleep.[7] PLMs were scored according to AASM criteria,[7] and the PLM index was defined as the number of PLMs per hour sleep.

Statistical analysis

Data are expressed as means with standard deviation (SD). The differences between manual and automated analyses were assessed using the method described by Bland and Altman,[23] and Student's t-test for paired samples. The sensitivity, specificity and positive and negative predictive values of automated analysis for diagnosing an obstructive sleep apnea-hypopnea syndrome (OSAHS) were calculated based on an AHI ≥ 5 and using the manual analysis as the gold standard. P values < 0.05 were considered statistically significant. All statistical analyses were carried out using the SPSS version 17.0 statistical package (SPSS, Inc., Chicago, IL).

Results

Fifty PSG recordings of patients with COPD and 57 PSG recordings of controls were used for the analyses. The characteristics of the subjects are shown in Table 1. Indications for the PSG in the group of COPD patients and the group of subjects without COPD were: difficulties initiating or maintaining sleep (44/14), OSAHS (4/26), evaluating continuous positive airway pressure (CPAP)-treatment (1/2), PLMs (1/0), excessive daytime sleepiness (0/13), unexplained tiredness (0/1), and convulsions (0/1).

Tables 2 and 3 show the findings from the PSGs in respectively the patients with and without COPD. Comparisons between manual and automated analysis of the PSG findings (i.e. results from the Bland-Altman analyses) are shown in Tables 4 and 5 for respectively patients with and without COPD.

The majority of compared sleep parameters showed statistically significant differences between the two methods, indicating low agreement. The automated analysis gave statistically significant overestimation of TST, number of arousals, the amount of REM sleep and stage 1 sleep. It underestimated stage 3 and 4 sleep and the no. of leg movements.

Table 1 Characteristics of the subjects

Variable	COPD (n=50)	No COPD (n=57)	P value
Age, yr	61.6 ± 7.8	52.8 ± 14.3	< 0.01
Sex, M (%)	38 (76)	34 (60)	0.07
BMI, kg/m^2	23.6 ± 5.1	31.9 ± 7.2	< 0.01
ESS	6 ± 4	14 ± 6	< 0.01
FEV_1, L	1.3 ± 0.9	3.0 ± 0.9	< 0.01
FEV_1, % predicted	41.4 ± 24.8	99.9 ± 19.2	< 0.01
FEV_1 / FVC	36.2 ± 16.1	78.3 ± 6.2	< 0.01
Reversibility of FEV_1, % predicted	3.1 ± 3.6	NA	NA
Baseline $PaCO_2$, kPa	5.4 ± 0.6	5.2 ± 0.6	0.16
Baseline PaO_2, kPa	9.4 ± 1.5	11.1 ± 2.0	< 0.01
Smoking status			
Yes, n	45	5	< 0.01
No, n	2	39	< 0.01
Former, n	3	13	< 0.01
pack-years, yrs	43 ± 16	8 ± 6	< 0.01

Data are expressed as mean ± SD, unless stated otherwise. BMI: body mass index; COPD: chronic obstructive pulmonary disease; ESS: Epworth sleepiness scale; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; NA = not applicable; $PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen.

Only the SE in subjects with and without COPD and the stage 2 sleep in subjects with COPD had differences that were not statistically significant. There were no major differences in outcomes between the subjects with COPD and those without COPD. When looking at the respiratory parameters, agreement between the two methods was also poor. Automated analyses overestimated the AHI due to overestimation of the number of apneas/hour. In Figure 1 a Bland-Altman plot showing the difference in AHI between the two methods versus the mean of the AHI is shown. The AHI was chosen to plot because it is a variable that is regularly used in common practice. Sensitivity for diagnosing OSAHS (AHI ≥ 5) with the automated analysis was 91.7%, specificity 40.4%, the positive predictive value 66.3% and the negative predictive value was 79.2%

Table 2 Polysomnographic findings of manual and automated analyses in patients with COPD

	Manual	Automatic	P value
Total sleep time (hr)	6.0±1.2	7.4±0.6	< 0.01
Sleep-onset latency (min)	27.4±27.0	5.2±7.8	< 0.01
REM sleep latency (min)	136.0±76.8	42.0±51.3	< 0.01
Sleep efficiency (%)	82.6±12.8	85.1±13.5	0.33
Arousal index (/hr)	6.1±4.2	11.3±11.0	< 0.01
REM sleep (min)	48.1±34.0	135.3±79.3	< 0.01
Stage 1 sleep (min)	88.6±50.7	139.0±70.2	< 0.01
Stage 2 sleep (min)	156.0±56.9	149.8±74.1	0.64
Stage 3 sleep (min)	42.6±21.8	14.3±24.7	< 0.01
Stage 4 sleep (min)	24.2±19.8	0.1±0.1	< 0.01
Leg movements (/hr)	23.3±20.8	1.1±7.6	< 0.01
AHI (/hr)	10.5±15.7	19.1±15.2	< 0.01
ODI (/hr)	12.3±14.6	10.5±13.4	0.04
Mean SpO_2 (%)	92.0±2.8	92.1±2.7	0.29
Apnea index (/hr)	4.3±9.8	14.9±13.6	< 0.01
Hypopnea index(/hr)	6.2±6.8	3.7±4.4	< 0.01
Mean heart rate (/min)	81.1±26.4	80.1±25.7	0.69

Data are expressed as mean ± SD; COPD: chronic obstructive pulmonary disease; AHI: apnea-hypopnea-index; ODI: oxygen desaturation index; SpO_2: functional saturation of oxygen.

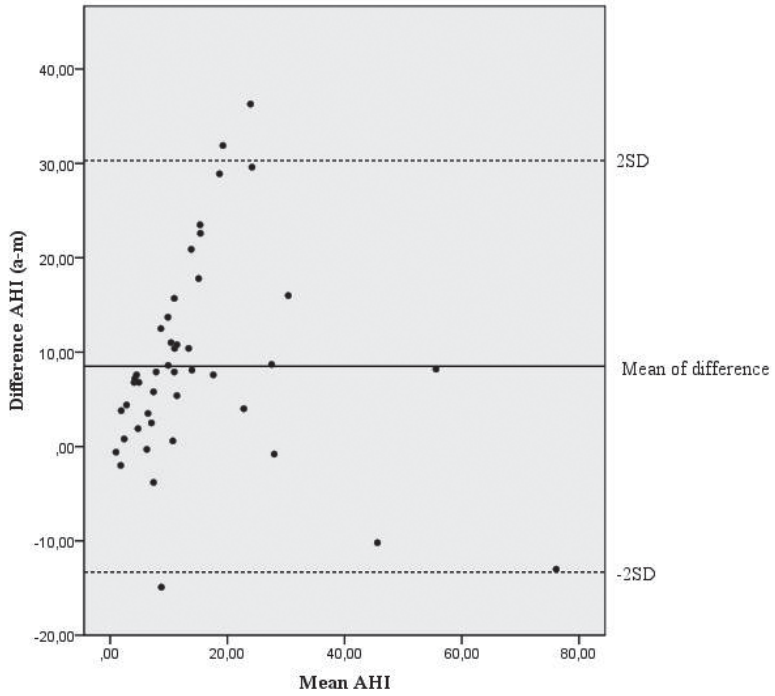

Figure 1 Bland-Altman plot: agreement of AHI in patients with COPD.

Dots represent absolute differences versus mean values for the apnea-hypopnea-index (AHI) assessed manually and automatically. The solid line represents the mean of the differences (=bias) between manually and automatically assessed AHI (8.5 events /hr). The dashed lines are equivalent to 2 standard deviations of the mean (= 95% limits of agreement); m: manual analysis; a: automatic analysis.

Table 3 Polysomnographic findings of manual and automated analyses in patients without COPD

	Manual	Automatic	P value
Total sleep time (hr)	6.6±1.0	7.5±0.8	< 0.01
Sleep-onset latency (min)	28.0±31.0	9.4±18.9	< 0.01
REM sleep latency (min)	123.9±95.8	49.9±70.2	< 0.01
Sleep efficiency (%)	89.1±13.5	89.4±5.7	0.88
Arousal index (/hr)	5.1±5.2	8.7±9.1	< 0.01
REM sleep (min)	54.4±32.6	103.8±53.2	< 0.01

Table 3 Continued

	Manual	Automatic	P value
Stage 1 sleep (min)	66.2±39.5	159.0±77.7	< 0.01
Stage 2 sleep (min)	204.9±55.0	155.0±55.7	< 0.01
Stage 3 sleep (min)	47.6±27.6	22.8±32.8	< 0.01
Stage 4 sleep (min)	25.7±22.2	0.8±4.1	< 0.01
Leg movements (/hr)	20.5±25.8	0.02±0.1	< 0.01
AHI (/hr)	15.1±16.2	18.1±15.8	< 0.01
ODI (/hr)	15.1±15.8	16.4±15.4	0.04
Mean SpO_2 (%)	94.3±3.1	94.4±2.9	0.12
Apnea index (/hr)	8.1±14.7	15.6±14.6	< 0.01
Hypopnea index (/hr)	6.8±6.1	3.0±4.8	< 0.01
Mean heart rate (/min)	66.5±17.6	67.6±17.4	0.02

Data are expressed as mean ± SD; AHI: apnea-hypopnea-index; COPD: chronic obstructive pulmonary disease; ODI: oxygen desaturation index; SpO_2: functional saturation of oxygen.

Table 4 Agreement of polysomnographic findings between manual and automated analyses in patients with COPD

	Bias	Precision	95% Limits of agreement
Total sleep time (hr)	1.4	1.2	-1.0 to 3.8
Sleep-onset latency (min)	-22.2	29.6	-51.4 to 37
REM sleep latency (min)	-94.0	85.1	-264.2 to 76.2
Sleep efficiency (%)	2.6	18.2	-33.8 to 39.0
Arousal index (/hr)	5.1	10.9	-16.7 to 26.9
REM sleep (min)	87.2	82.1	-77.0 to 251.4
Stage 1 sleep (min)	50.4	79.9	-109.4 to 210.2
Stage 2 sleep (min)	-6.2	91.8	-189.8 to 177.4
Stage 3 sleep (min)	-28.3	33.2	-94.7 to 38.1
Stage 4 sleep (min)	-24.2	19.9	-64.0 to 15.6
Leg movements (/hr)	-22.1	21.7	-65.5 to 21.3
AHI (/hr)	8.5	10.9	-13.3 to 30.3
ODI (/hr)	-1.8	5.6	-13.0 to 9.4

Table 4 Continued

	Bias	Precision	95% Limits of agreement
Mean SpO_2 (%)	0.1	0.9	-1.7 to 1.9
Apnea index (/hr)	10.6	10.0	-9.4 to 30.6
Hypopnea index (/hr)	-2.5	5.7	-13.9 to 8.9
Mean heart rate (/min)	-1.1	9.0	-19.1 to 16.9

Data are expressed as mean ± SD. AHI: apnea-hypopnea-index; Bias = mean difference (automatic – manual analysis); COPD: chronic obstructive pulmonary disease; ODI: oxygen desaturation index; Precision = SD of mean difference; SpO_2: functional saturation of oxygen; 95% Limits of agreement = bias ± 2 SD.

Table 5 Agreement of polysomnographic findings between manual and automated analyses in patients without COPD

	Bias	Precision	95% Limits of agreement
Total sleep time (hr)	0.8	1.0	-1.2 to 2.8
Sleep-onset latency (min)	-18.6	36.4	-91.4 to 54.2
REM sleep latency (min)	-74.0	115.3	-304.6 to 156.6
Sleep efficiency (%)	0.26	13.1	-25.9 to 26.5
Arousal index (/hr)	3.6	8.6	-13.6 to 20.8
REM sleep (min)	49.4	56.3	-63.2 to 159.0
Stage 1 sleep (min)	92.8	81.6	-70.4 to 256.0
Stage 2 sleep (min)	-50.1	69.0	-188.1 to 87.9
Stage 3 sleep (min)	-24.8	40.0	-104.8 to 55.2
Stage 4 sleep (min)	-24.9	21.8	-68.5 to 18.7
Leg movements (/hr)	-20.5	25.8	-72.1 to 31.1
AHI (/hr)	3.0	6.2	-9.4 to 15.4
ODI (/hr)	1.3	4.6	-7.9 to 10.5
Mean SpO_2 (%)	0.1	0.3	-0.5 to 0.7
Apnea index (/hr)	7.5	6.4	-5.3 to 20.3
Hypopnea index (/hr)	-3.8	4.5	-12.8 to 5.2
Mean heart rate (/min)	1.1	1.2	-1.3 to 3.5

Data are expressed as mean ± SD. AHI: apnea-hypopnea-index; Bias = mean difference (automatic – manual analysis); COPD: chronic obstructive pulmonary disease; ODI: oxygen desaturation index; Precision = SD of mean difference; SpO_2: functional saturation of oxygen; 95% Limits of agreement = bias ± 2 SD.

Discussion

This study demonstrates that automated analysis of PSG recordings, as measured with the used automated system, in patients with and without COPD have poor agreement with manual analysis (the gold standard). The majority of outcomes of automated analysis of sleep parameters were statistically significantly different from outcomes of manual analysis. There was also a poor agreement regarding respiratory parameters; automated analysis overestimated the AHI (with > 8 events/hr sleep) when compared to the manual analysis and as a consequence the sensitivity for diagnosing OSAHS with this system was high, but specificity was low.

Because the agreement was poor in both study groups, it was in our view irrelevant to compare the extent of (dis)agreement with each other (i.e. to assess which group expressed the most disagreement).

The disagreement between the manual and the automated analysis can be caused by previously described causes like difficulties to distinguish both REM sleep and nREM stage 2 sleep from nREM stage 1 sleep, and difficulties to acknowledge subtle changes in the recordings.[11,12,24] In addition, for the calculation of several parameters the efficient sleep time is used. So when the measured amount of sleep time is not the true sleep time (as determined by manual analysis), this affects other parameters as well. Another factor that may negatively affect performance of automated analysis is that more disturbed sleep, with frequent sleep stage shifts, arousals, and movements artefacts, may influence the degree of agreement between the two types of analysis.

A strength of this study was the use of patients with sleep problems as subjects instead of healthy humans without any sleep problems. In addition, we examined several components of PSG scoring such as sleep staging, respiratory events, arousals and PLMs instead of only one of these components.

One of the limitations of the present study was that we did not assess the agreement epoch-by-epoch. Such an analysis would have been more accurate, but we wanted to assess the automated system in a situation closest to day-to-day clinical practice. Furthermore, we only assessed one analytic system, so the current results should not be applied to other currently available automated systems. . And even though the manual analysis is regarded as the gold standard, the manual analysis has been subject to some interobserver variability. Interobserver agreement has previously been reported as 88%,[17] between 65-78%,[25] 77%,[26] and between 78-88%.[27]

This study was not designed to investigate the sleep quality of patients with COPD. Since the characteristics of the subjects with and without COPD differed from each other, it would not be correct to compare the two study groups with each other. And since all patients with COPD were having sleep problems (there was a clinical reason to perform the PSG), the PSG outcomes in the COPD group may not be

representative for patients with COPD in general. Nevertheless, the quality of sleep in the studied COPD patients was poor with a TST of 6.0 hours, a SE of 82.6% and a duration of REM sleep of 48.1 minutes (13% of TST). These findings are comparable with earlier findings of poor sleep quality in patients with COPD.[2]

This is to our knowledge the first study to evaluate the reliability of an automated scoring system of PSGs in patients with COPD. Previous studies assessed the agreement of automated analysis in healthy subjects,[9] in subjects with suspected sleep-disordered breathing,[14,15] in depressed and insomniac patients,[17] and in children.[18] Some of these studies reported good agreement,[8-10,17,19] while others did not.[11-15,18] An explanation for the differences between this study and others might be the study population; most of the previous studies have been performed in healthy or otherwise selected populations, a few have used subjects with disturbed sleep. Other explanations might be in differences in the studied computer systems and the way manual analysis was performed (i.e. with or without pre-processing).

Automated analysis could still be useful in PSGs, because it provides additional information like apnea duration, lowest SpO_2, time spent with $SpO_2 < 90\%$, body position, snoring quantification, etcetera. And perhaps, when future computerized scoring systems do provide reliable results, these systems can reduce workload and shorten waiting lists.

In conclusion, we compared the manual analysis of PSG recordings of patients with COPD to automated analysis by two sleep specialists and found that automated analysis, as measured with the used system, does not produce reliable outcomes and should therefore not replace the manual analysis of PSG recordings in patients with and without COPD. Future studies examining the reliability of newer automated systems (as complete analysis or as pre-processor before manual analysis takes place) are needed before automated systems can reliable be used in the analysis of PSG recordings in patients with COPD.

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Conflict of Interest Statement

None of the authors has potential conflicts of interest.

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SMOKE
FREE
ZONE

7

Summary and general discussion

Summary

This thesis is about the sleep in patients with COPD; it describes the sleep quality, the respiratory function during sleep and the effects of sleep medication on the respiratory function in patients with COPD.

The main findings of this thesis are the following: The sleep of patients with chronic obstructive pulmonary disease (COPD) is often of poor quality **(chapter 2)**. Up to fifty-three percent of patients with COPD report sleep-related complaints characterized by a longer sleep latency, more frequent arousals and awakenings, and more daytime sleepiness than healthy individuals. Polysomnographic recordings in patients with COPD show reductions in total sleep time (TST) and duration of slow wave and rapid eye movement (REM) sleep, more sleep state changes, and an increase in number and severity of arousals during sleep. Benzodiazepines and non-benzodiazepine benzodiazepine-receptor agonists (NBBRAs) seem to be equally effective in treating insomnia and these drugs can all produce undesirable effects like drowsiness, dependence, rebound insomnia, memory impairment, and adverse effects on the respiratory function. Regarding these adverse effects on respiratory function, only distinct differences exist between NBBRAs and benzodiazepines **(chapter 2)**. A meta-analysis is needed to compare the adverse effects of benzodiazepines and NBBRAs on respiration with each other, but such a meta-analysis is difficult to carry out due to the wide variation in available studies. In healthy people the adverse effects on respiratory function of benzodiazepines are very moderate and therefore could be tolerated in this population. Comparable changes are seen in patients with COPD, but it remains unclear if these can be tolerated as well **(chapter 2)**. Consequently, the use of benzodiazepines in these patients should be as short as possible.

Physicians should keep in mind that up to 50% of their patients with COPD may experience sleep abnormalities. By asking for sleeping complaints and understanding the pathophysiology and available treatment options for these problems, they have a great tool to substantially improve their patients' quality of life.

Although guidelines advise against the use of sleep medication in patients with COPD, more than 20% of patients with COPD use sleep medication **(chapter 3)**. They use it as often as matched patients with diabetes mellitus (DM) and healthy controls. This finding implies that the currently available non-pharmacological therapies do not suffice for sleep related complaints in patients with COPD. The most frequently prescribed drugs to promote sleep were temazepam, oxazepam, diazepam, and zolpidem. The prescribed hypnotics do not differ between the study groups **(chapter 3)**.

In this thesis the reliability and usability of a transcutaneous monitor to reflect the partial pressure of carbon dioxide (PCO_2) and the functional saturation of oxygen

(SpO_2) during exercise tests was studied in patients with various pulmonary diseases **(chapter 4)**. PCO_2 and SpO_2 values can accurately be assessed by a transcutaneous sensor during an exercise test when compared to arterial measurements of PCO_2 and SpO_2 **(chapter 4)**. The transcutaneous capnometer is easy to use with low burden for the patient. A limitation of its use is the absence of other informative indices like bicarbonate, lactate, and PaO_2. When these indices are of interest, transcutaneous measurements can obviously not replace arterial samples. So when the transcutaneous sensor is used during an exercise test in combination with the measurement of expired gases and minute ventilation, indices of cardio respiratory quality can be assessed in selected cases and arterial cannulation can be avoided. Since the transcutaneous sensor provides accurate results during an unstable situation like exercise, the sensor will almost certainly provide accurate measurements of PCO_2 during sleep.

Repeated doses of the benzodiazepine temazepam did not adversely affect nocturnal respiratory function in severe but stable normocapnic COPD patients in a preliminary study **(chapter 5)**. Temazepam did not affect diurnal gas exchange, diurnal central respiratory centres, and subjective dyspnea. In the treatment of sleep-related complaints in patients with stable normocapnic COPD, temazepam can in our view not automatically be dismissed. Its safety should however be confirmed in larger studies. Until those studies are performed, temazepam remains to be seen as a last resort when other, non-pharmacological remedies have failed **(chapter 5)**.

The analysis of polysomnographic recordings in patients with and without COPD by an automated system gives outcomes with a large bias and low precision when compared to outcomes by manual analysis (the gold standard) **(chapter 6)**. Although an automated analysis of a polysomnography is less time-consuming and therefore cheaper than manual analysis, its outcome is inaccurate and inferior to the outcome of manual analysis of a polysomnography. These findings make the use of only an automated system for the analysis of polysomnographic recordings unfavourable **(chapter 6)**.

Unfortunately there is still doubt on several issues. The clinically most relevant issues are whether other benzodiazepines than temazepam can safely be used in patients with COPD, whether temazepam can safely be used in other situations like during exacerbations of COPD or in patients with other pulmonary diseases than COPD, whether other (non-pharmaceutical) treatment options can improve the sleep quality in patients with COPD, and whether factors like nocturnal hypoxemia, inspiratory muscle performance, cardiovascular co-morbidity, pulmonary function, smoking status, anxiety/depression play a role in the sleep problems in patients with COPD. These issues should be key future research topics in this field of medicine.

General discussion

This thesis gives an overview of the effects of sleep on respiratory function, the effects of COPD on sleep, and the effects of sleep medication on respiration **(chapter 2)**. It also describes the epidemiology of sleep medication use in patients with COPD **(chapter 3)**, the effects of the sleeping drug temazepam on respiratory function in patients with COPD **(chapter 4)**, the validation of a method to measure transcutaneously PCO_2 in order to assess respiratory function during sleep **(chapter 5)**, and it compares two methods for examining polysomnographic recordings in patients with COPD **(chapter 6)**.

Sleep and COPD

The sleep quality of patients with COPD can severely be diminished **(chapter 2)**. More than 50% of patients with COPD experience sleep-related complaints.[1] These complaints are ranked third, after dyspnea and fatigue, in frequency of complaints of patients with COPD.[2] It seems there is no relationship between the lung function and the prevalence of sleep problems in these patients.[3] However, the prevalence of sleep problems seems to be related to the quantity and severity of pulmonary complaints.[3]

Several factors contribute to the development of sleep problems in COPD. These are the supine position, cough and excessive mucus production during sleep, altered ventilation/perfusion (V/Q) relationships, the increased ventilatory effort during sleep, and the nocturnal desaturations and hypercapnic episodes that occur during sleep **(chapter 2)**. Other factors that might negatively influence the sleep quality in COPD are cardiovascular co-morbidity, smoking status, and psychiatric co-morbidities like anxiety and depression.

Another interesting finding in chapter 2 was that a single night's loss of sleep results in significant, but clinically not relevant reductions of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) in patients with COPD.[4] On the one hand, this finding may imply that the long-term pulmonary function can be negatively affected by multiple nights of sleep deprivation. On the other hand, it could be that worsening the pulmonary function further worsens the present sleep problems. Or perhaps a common cause (e.g. smoking, co-morbidities) exists for both the sleep problems and reduction of the pulmonary function. This cause-effect question should be further investigated.

Omachi et al. showed that the occurrence of sleep problems in patients with COPD is associated with an increased mortality.[5] It is unclear whether sleep problems are directly responsible for this increased mortality, or that another factor is both

causing sleep problems and causing this increase in mortality. Further research might clarify this question.

Sleep medication

Since COPD patients experience sleep problems often, they may frequently ask for sleep medication during a doctor's visit. Even though it seems tempting to comply with such a request, prescribing sleep medication should be done cautiously to patients with COPD. Sleep medication might have a negative effect on the respiratory function during sleep, both in subjects with and without COPD **(chapter 2)**. Guidelines of the American Thoracic Society (ATS) and European Respiratory Society (ERS) state that sleep medication should be avoided in patients with severe COPD.[6] This advise is based on studies that found modest unfavourable effects on respiration from sleep medication.[7-11] Benzodiazepines and non-benzodiazepine benzodiazepine-receptor agonists (NBBRAs) may have negative side effects. They decrease the central sensitivity to hypoxic and hypercapnic stimuli, they may decrease the arousal response following hypoxemia or hypercapnia, and they may increase the upper airway resistance due to myorelaxation.[7-11] However, other studies did not find these unfavourable effects of sleep medication.[12-19] Unfortunately, these contradicting studies are difficult to compare with each other and have several factors that can be commented on. For instance the study periods differed from several hours during the daytime to a single night to several following nights of drug usage; patients without COPD or with diverse severity of COPD were included; diverse benzodiazepines with different pharmacological properties were used; and the respiratory outcome variables varied between these studies.

It is obvious that a meta-analysis is needed to answer the question: what is the effect of drugs that promote sleep on breathing during sleep in patients with COPD? At the same time it is obvious that performing such a meta-analysis would be comparing apples and oranges due to the major differences in the eligible studies. As a result such a meta-analysis would be troublesome to perform and interpret. The question can only be answered by performing a new study. This study should include patients with varying degrees of COPD and patients without COPD. Furthermore, the effects of not only one but multiple drugs that promote sleep with different pharmacological profiles should be compared with each other, and the study period of this study should be multiple connected nights.

The currently available studies show that, regarding the adverse effects of drugs that promote sleep on respiration, only little differences exist between short- and intermediate-acting benzodiazepines and the 'newer' NBBRAs like zaleplon, zolpidem and zopiclon. More adverse effects on respiration were seen with the longer-acting

benzodiazepines **(chapter 2)**. So based on the current evidence one particular sleeping drug cannot be advised in patients with COPD above any of the other available sleeping drugs. Nevertheless, it is recommended to use a short- or intermediate acting sleeping drug in order to reduce the risk of any (daytime) side-effects.

It is not advisable to prescribe any other drugs than a benzodiazepine or NBBRA to promote sleep, since the use of alternatives like sedating anti-depressants, antihistamines (like promethazine), melatonine and over-the-counter drugs to promote the sleep quality is not supported by evidence **(chapter 2)**.

To improve treatment options for patients with COPD, research is needed to elucidate the cause-effect relationship of various individual aspects (e.g. nocturnal hypoxemia, inspiratory muscle performance, cardiovascular co-morbidity, pulmonary function, smoking status, anxiety/depression) on sleep in patients with COPD.

The effects of commonly used pulmonary medication like β_2-agonists and anti-cholinergics on the sleep quality seem to be negligible.[20] Orally taken steroids might negatively influence the sleep quality,[21] but it is unknown whether inhaled steroids have adverse effects on sleep quality as well.

The extent of use of sleep medication was studied in a primary care population of patients with COPD, patients with diabetes mellitus (DM) and healthy subjects **(chapter 3)**. The use of sleep medication appeared to be substantial in patients with COPD (approximately 20%), but equal to the other two study groups. So although guidelines advise not to prescribe sleep medication to patients with COPD, a considerable proportion of patients with COPD did ever use sleep medication. It might be that physicians are not familiar with the possible adverse events associated with benzodiazepines, or that physicians ignore the ATS/ERS guidelines, perhaps because sleep problems are such a major complaint amongst patients with COPD. Future research is needed to investigate these assumptions about prescription-behaviour and to improve non-pharmaceutical treatment options for sleeping problems in these patients.

The benzodiazepine temazepam was the sleeping drug that was prescribed most frequent, followed by oxazepam and diazepam **(chapter 3)**. The frequencies of prescribing these benzodiazepines did not differ between the study groups.

Because a. the overall use of sleep medication in COPD remains considerable, b. these drugs may have negative effects on breathing and c. poor sleep quality results in poor quality of life, physicians should pay special attention towards sleep problems in patients with COPD. Furthermore, they should first focus on non-pharmacological treatment options before considering sleep medication.

Temazepam

The prolonged use of temazepam does not influence indices of breathing and gas exchange during sleep in patients with severe COPD who experience insomnia **(chapter 5)**. Furthermore, temazepam does not have any positive or negative effects on diurnal breathing, gas exchange, and dyspnea in patients with severe COPD and insomnia **(chapter 5)**.

Our findings imply that temazepam can safely be used by these patients without any adverse effects on respiration. This is an important finding because it provides patients and physicians a treatment option for sleeping problems without concerns of any unfavourable effects on breathing. Nevertheless, while prescribing temazepam physicians should be aware of the other side effects of temazepam and that its use is only recommended for up to one month.[22]

A study published in 2009[23] showed that ramelteon (a melatonin receptor agonist) is also safe to use in patients with moderate to severe COPD. However, in this study ramelteon was only used for one night, the $PtcCO_2$ was not assessed (the SpO_2 was used as the primary endpoint) and it is unclear whether the PSGs were manually analyzed.

The findings in chapter 5 do not immediately urge changes in guidelines on the use of sleep medication in patients with COPD. A weakness of the study in chapter 5 is the number of included subjects. Although the number of included subjects was sufficient to statistically significantly conclude that temazepam is safe in the whole group of patients with COPD, on an individual scale adverse effects might still occur. Some patients might be more susceptible than others to the adverse effects of temazepam. Therefore the study is called 'preliminary' and guidelines can only be modified after future research with larger numbers is done to include some of those 'more susceptible' patients.

Perhaps a to-be-made questionnaire can point out those 'more susceptible' patients. Such a questionnaire should be a topic for further research. It might for instance be that patients with COPD who are more than others at risk for hypoxaemia during sleep share risk factors with those who are more susceptible for adverse effects of a benzodiazepine. Vos et al. described patients with COPD who are more at risk for nocturnal hypoxaemia.[24] Future research should be done to investigate what the risk factors are for developing the adverse effects of benzodiazepines in healthy subjects and in patients with COPD.

Physicians should be aware that the findings in chapter 5 do not apply to other, related situations such as the use of other benzodiazepines, larger doses of temazepam, patients with an exacerbation of their COPD, hypercapnic COPD or COPD plus a sleep apnea-syndrome or patients with another pulmonary disease. For instance, benzodiazepines are not only used to promote sleep; they are also sometimes used to reduce anxiety. For this indication, often longer-acting benzodiazepines like

oxazepam are used. It remains unclear whether these benzodiazepines can safely be used in patients with COPD.

Future studies should be done to examine the safety of temazepam and other benzodiazepines and NBBRAs in patients with COPD and the aforementioned conditions. Until those studies are carried out, temazepam and other sleep medication should be used with caution in patients with COPD and only when non-pharmacological therapies have failed.

One of the key targets for future research should be other, non-pharmacological therapies for the treatment of sleeping problems in patients with COPD. Until now only one study assessed cognitive behavioural therapy for sleeping problems in patients with COPD.[25] That study showed that cognitive behavioural therapy improved the sleep quality in patients with COPD. However, the study was underpowered and only studied short-term effects of the therapy. The study shows that cognitive behavioural therapy seems to be a promising treatment, but it has to be examined more extensively.

Before commencing sleep medication, the primary step in the treatment of sleeping problems in patients with COPD should be to optimize their regular COPD therapy and advise them to stop smoking. The incidence of sleeping problems in patients with COPD is associated with respiratory complaints and smoking (but again, a causative relation has not been found yet).[20]

Carbon dioxide

The agreement between arterial en transcutaneous carbon dioxide values (respectively $PaCO_2$ and $PtcCO_2$) during CPET as measured with the used sensor is clinical acceptable **(chapter 4)**. Recently, other studies have been published on the use of the $PtcCO_2$-sensor in several other settings, like during non-invasive ventilation,[26,27] and at the emergency room.[28] The sensor was not studied during sleep because of a practical obstacle; subjects were not expected to continue their sleep when an arterial puncture was performed or when a blood sample from an indwelling arterial catheter was taken. Therefore we chose a setting which suited well for comparing $PaCO_2$ and $PtcCO_2$ with each other: a cardiopulmonary exercise test (CPET). And since the sensor provides accurate results when subjects are in an unstable respiratory situation like CPET, it is likely that it will function well when subjects are more stable like when asleep. Other studies examined the performance of the sensor over a prolonged period of time; the sensor provided accurate results in an intensive care setting.[29,30] Thus it is assumed that the accuracy of the sensor is as good during sleep as it is in the intensive care, since the setting of sleep (body position, state of awareness, length of measurement) is comparable with the setting of an intensive care.

The ability to accurately measure PCO_2 during sleep is an important improvement in assessing the respiratory function during sleep, since the PCO_2 strongly correlates

to the quality of ventilation. The findings in chapter 4 provide a better method to evaluate ventilation during sleep than the methods used in previous studies.

Polysomnography

We assessed the agreement between automated analysis of polysomnographies (PSGs) and manual analysis of PSGs (the gold standard) **(chapter 6)**. It was thought that progress in electronics and engineering provided means to overcome the burden of manual data-analysis. This 'burden' regards to the time-and personnel consuming labour of analyzing the large amount of data gathered during a PSG.

Automated analysis of PSG recordings in patients with (and also in those without) COPD has poor agreement with manual analysis **(chapter 6)**. The agreement was poor in both the sleep variables and the respiratory variables. This disagreement has implications for clinicians. For instance a bias in total sleep time of 1.4 hours is a clinically relevant difference. And a bias in apnea-hypopnea index of 8.5 events per hour could mean the difference between being diagnosed as having a sleep-apnea syndrome or not. This disagreement is probably caused by difficulties to distinguish several sleep stages from each other (mainly REM sleep and nREM stage 2 sleep from nREM stage 1 sleep), which is due to complexities to acknowledge subtle changes in the recordings.

Earlier studies examined the agreement of automated analysis with manual analysis in the following subject-groups: healthy subjects,[31] subjects with suspected sleep-disordered breathing,[32,33] depressed and insomniac patients,[34] and children.[35] Some of these studies reported good agreement,[31,34,36-38] while others did not.[32,33,35,39-41] These discrepancies in agreement show that it is not apparent to use automated analyses of PSGs in research and in clinical practice in every subject group. The accuracy of automated analyses should be examined in every subgroup of patients with known disturbed sleep, like patients with heart diseases, depression, hypertension, end-stage renal failure, diabetes mellitus, stomach ulcers, arthritis, migraine and other neurological problems, asthma, COPD, and menstrual problems.[42]

It is worrying that the automated system for PSG analysis might have been used in several studies, like one mentioned above.[23] Most, but not all studies did report how the PSG-data have been analysed. To avoid any obscurities, future papers should state how the PSG-data were analysed.

Perhaps automated analysis could be used after all; not as a full replacement of manual analysis, but as an addition. In several studies[38,43,44] a semi-automated system was incorporated in the analysis: the PSG data were initially 'pre-processed' by an automated system, after which a person manually analysed these 'pre-processed' data. Whether there is a role for automated analysis of PSGs in the future needs to be established when improved automated systems become available.

Recommendations

The non-pharmaceutical treatment options for sleeping problems in patients with COPD should be improved. One of these treatment options is for instance cognitive behavioural therapy. The role of cognitive behavioural therapy in the treatment of sleep problems in patients with COPD should further be examined. Furthermore, physicians should be made more aware of the importance of sleep hygiene. They should give sleep hygiene advises before prescribing sleep medication to patients with COPD.

Future research should be done to investigate what the risk factors are for developing sleep problems in patients with COPD and for developing adverse effects of benzodiazepines on respiration in these patients.

The preliminary results from chapter 5 should be confirmed in a study with a larger population, including some of the 'more susceptible to temazepam and/or other benzodiazepine' patients with COPD, with varying degrees of COPD and with patients without COPD, comparing various drugs that promote sleep with different pharmacological profiles with each other, and with a study period of multiple connected nights. Only then guidelines on the use of benzodiazepines in patients with COPD can be changed.

Studies should be done to examine the safety of temazepam and other benzodiazepines and NBBRAs in patients with an exacerbation of their COPD, with hypercapnic COPD, in patients with COPD plus a sleep apnea-syndrome or in patients with another pulmonary disease.

In the end, the sleep quality in patients with COPD can severely be disturbed and physicians should pay special attention towards sleep problems in these patients, because improvements in sleep quality will have a favourable impact on the quality of life in patients with COPD with sleeping problems. Treatment options for these sleep problems are not only non-pharmaceutical, but the benzodiazepine temazepam can safely be used to promote sleep without any adverse effects on the respiratory function.

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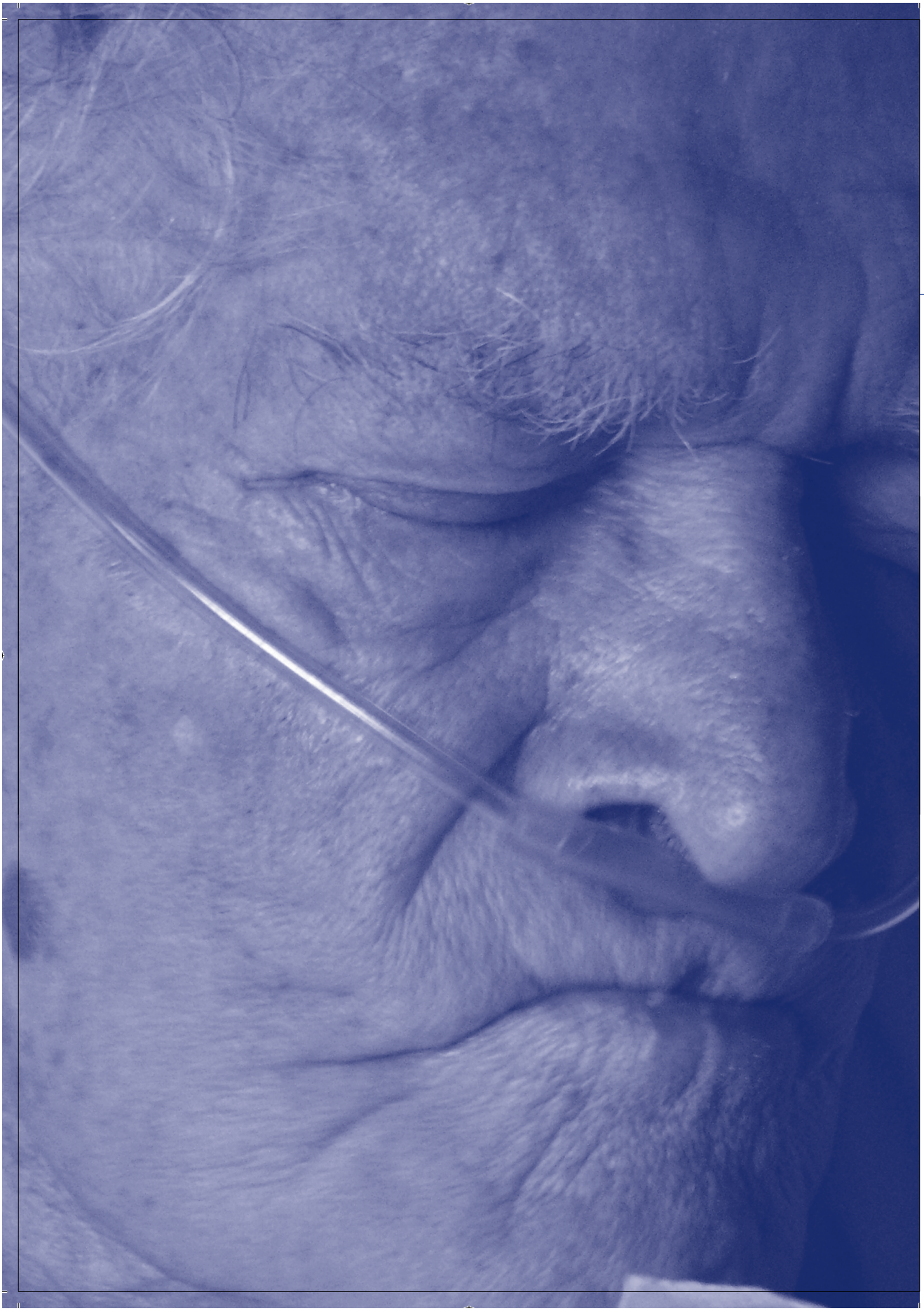

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Samenvatting en algemene discussie (Dutch)

Samenvatting

Dit proefschrift gaat over de slaap bij patiënten met COPD; het beschrijft de kwaliteit van de slaap, de ademhaling tijdens de slaap en de effecten van slaapmiddelen op de respiratoire functie bij patiënten met COPD.

De belangrijkste bevindingen van dit proefschrift zijn de volgende: de slaapkwaliteit van patiënten met COPD is vaak slecht **(hoofdstuk 2)**. Tot drieënvijftig procent van de patiënten met COPD ervaren slaapklachten, die bestaan uit een verlengde slaaplatentie, meer 'arousals' en tussentijds wakker worden en meer slaperigheid overdag dan gezonde mensen. Polysomnografieën tonen een afname in totale slaaptijd (TST), afname van de duur van lage golf slaap en 'rapid eye movement' (REM) slaap, meer slaap stadium wisselingen en een toename in het aantal en ernst van 'arousals' tijdens de slaap van mensen met COPD. Benzodiazepines en non-benzodiazepine benzodiazepine-receptor agonisten (NBBRAs) lijken even effectief in de behandeling van slapeloosheid en al deze medicijnen kunnen nadelige bijwerkingen hebben zoals sufheid, afhankelijkheid, 'rebound' slapeloosheid, geheugenstoornissen en nadelige effecten op de ademhaling tijdens de slaap. Er zijn nauwelijks verschillen tussen de verschillende benzodiazepines en NBBRAs qua nadelige effecten op de ademhaling **(hoofdstuk 2)**. Een meta-analyse is nodig om de nadelige effecten op de ademhaling van de verschillende benzodiazepines en NBBRAs met elkaar te vergelijken. Een dergelijke meta-analyse is echter lastig uit te voeren door de grote variatie in de reeds verrichte studies. Bij gezonde mensen zijn de nadelige effecten op de ademhaling van benzodiazepines mild en daarom acceptabel. Benzodiazepines hebben vergelijkbare effecten op de ademhaling bij mensen met COPD, maar het is onduidelijk of deze effecten ook bij mensen met COPD acceptabel zijn **(hoofdstuk 2)**. Daarom zou het gebruik van benzodiazepines bij deze groep zo kort mogelijk moeten zijn.

Artsen moeten in hun achterhoofd houden dat meer dan 50% van hun patiënten met COPD slaapklachten kunnen hebben. Door te vragen naar slaapklachten en kennis te hebben van de pathofysiologie en behandelmogelijkheden van deze klachten, hebben ze een belangrijk middel om de kwaliteit van leven van deze patiënten te verbeteren.

Alhoewel richtlijnen het gebruik van slaapmiddelen bij mensen met COPD afraden, gebruikt meer dan 20% van deze patiënten een slaapmiddel **(hoofdstuk 3)**. Ze gebruiken het even vaak als 'gematchte' patiënten met diabetes mellitus (DM) en gezonde personen. Deze bevinding duidt erop dat de huidige niet-farmacologische behandelingen niet voldoende effectief zijn tegen slaapklachten bij mensen met COPD. De meest frequent aan mensen met COPD voorgeschreven slaapmiddelen waren temazepam, oxazepam, diazepam en zolpidem. Er waren geen verschillen tussen de studiegroepen qua voorgeschreven slaapmiddelen **(hoofdstuk 3)**.

In dit proefschrift werd ook de betrouwbaarheid en handzaamheid van een transcutane sensor om de koolzuurspanning (pCO_2) en de zuurstofsaturatie (SpO_2) te meten tijdens inspanningstesten bij patiënten met verschillende longziekten onderzocht **(hoofdstuk 4)**. Arteriële metingen van pCO_2 en SpO_2 werden beschouwd als de gouden standaard. Uit dit onderzoek bleek dat de pCO_2 en SpO_2 waarden nauwkeurig kunnen worden gemeten door de transcutane sensor tijdens een inspanningstest **(hoofdstuk 4)**. The transcutane sensor is makkelijk in het gebruik en weinig belastend voor de patiënt. Een beperking van de sensor is dat hij de waarden van andere informatieve stoffen, zoals bicarbonaat, lactaat, en de arteriële zuurstofspanning, niet kan meten. Als het van belang is ook deze waarden te meten, kunnen de transcutane metingen arteriële metingen uiteraard niet vervangen. Als de transcutane sensor wordt gebruikt tijdens een inspanningstest, in combinatie met de metingen van uitademinggassen en ventilatie, kan in geselecteerde gevallen de cardiorespiratoire kwaliteit betrouwbaar gemeten worden terwijl een arteriële punctie of lijn vermeden wordt. Omdat de transcutane sensor betrouwbare resultaten geeft tijdens een instabiele situatie zoals tijdens een inspanningstest, zal diezelfde sensor waarschijnlijk ook betrouwbare metingen van de PCO_2 geven tijdens slaap.

Herhaalde doses van de benzodiazepine temazepam beïnvloedden niet nadelig de ademhaling tijdens de slaap bij mensen met stabiel, ernstig COPD in een eerste studie **(hoofdstuk 5)**. Temazepam had geen nadelige effecten op de gaswisseling overdag, het functioneren van het ademhalingscentrum overdag of op de kortademigheid. Bij de behandeling van slaapklachten van mensen met stabiel, normocapnisch COPD kan temazepam niet automatisch terzijde worden geschoven. Echter, de veiligheid van temazepam zal in grotere studies bevestigd moeten worden. Totdat die grotere studies verricht zijn zal temazepam gezien moeten worden als een laatste redmiddel nadat andere, niet-farmacologische behandelingen geprobeerd zijn **(hoofdstuk 5)**.

De uitkomsten van analyse van polysomnografieën bij patiënten met en zonder COPD door een geautomatiseerd systeem zijn zeer verschillend ten opzichte van de uitkomsten van een handmatige analyse (de gouden standaard) **(hoofdstuk 6)**. Dus ondanks dat een automatische analyse van een polysomnografie minder tijd kost en goedkoper is dan een handmatige analyse, zijn de resultaten minder betrouwbaar. Daardoor is het analyseren van polysomnografieën door alleen een geautomatiseerd systeem onverstandig **(hoofdstuk 6)**.

Helaas is er nog steeds twijfel over verschillende onderwerpen. De klinisch meest relevante thema's zijn of andere benzodiazepines en NBBRAs dan temazepam veilig gebruikt kunnen worden door mensen met COPD, of temazepam veilig gebruikt kan worden in andere situaties, zoals tijdens een exacerbatie van de COPD en bij patiënten met een andere longziekte dan COPD, of andere (niet-farmacologische) behandelingen de slaapkwaliteit van mensen met COPD kunnen verbeteren, en of

factoren als nachtelijke hypoxemie, inspiratoire spierkracht, cardiovasculaire comorbiditeit, longfunctie, roken, en angst of depressie een rol spelen bij de slaapproblemen bij mensen met COPD. Deze kwesties zijn belangrijke toekomstige onderzoeksthema's in dit gebied van de geneeskunde.

Algemene discussie

Dit proefschrift geeft een overzicht van de effecten van slaap op de ademhaling, de effecten van COPD op de slaap, en de effecten van slaapmiddelen op de ademhaling **(hoofdstuk2)**. Het beschrijft ook de epidemiologie van het gebruik van slaapmiddelen door mensen met COPD **(hoofdstuk 3),** de effecten van het slaapmiddel temazepam op de ademhaling bij mensen met COPD **(hoofdstuk 4)**, de validatie van een methode om transcutaan pCO_2 te meten om zodoende de ademhaling tijdens de slaap te beoordelen **(hoofdstuk 5)**, en het vergelijkt twee methoden om een polysomnographie te beoordelen bij mensen met COPD **(hoofdstuk 6)**.

Slaap en COPD

De kwaliteit van de slaap bij mensen met COPD kan fors verlaagd zijn **(hoofdstuk 2)**. Meer dan 50% van de mensen met COPD ervaart slaapklachten.[1] Deze klachten bekleden de derde positie, achter dyspnoe en moeheid, op de lijst van meest voorkomende klachten bij mensen met COPD.[2] Er is waarschijnlijk geen relatie tussen de longfunctie en het voorkomen van slaapklachten bij deze patiënten.[3] Het voorkomen van slaapklachten lijkt echter wel gerelateerd te zijn aan de hoeveelheid en ernst van pulmonale klachten.[3]

Meerdere factoren spelen mee bij het ontstaan van slaapklachten bij COPD. Deze factoren zijn de horizontale positie, hoest en sputum productie tijdens de slaap, veranderde ventilatie/perfusie (V/Q) verhoudingen, de toegenomen inspanning om te ademen tijdens de slaap en nachtelijke desaturaties en hypercapnische episodes die optreden tijdens slaap **(hoofdstuk 2)**. Andere factoren die mogelijk een negatieve invloed hebben op de slaapkwaliteit bij mensen met COPD zijn cardiovasculaire comorbiditeiten, roken en psychiatrische aandoeningen zoals angst en depressie. Een andere interessante bevinding in hoofdstuk 2 is dat één nacht van slechte slaap al resulteert in een significante, maar klinisch niet relevante afname van het geforceerd expiratoir volume in 1 seconde (FEV_1) en geforceerde vitale capaciteit (FVC) bij patiënten met COPD.[4] Aan de ene kant kan deze bevinding betekenen dat de longfunctie op de lange termijn negatief beïnvloed kan worden door meerdere nachten van slechte slaap. Aan de andere kant kan het zijn dat een verslechtering

van de longfunctie aanwezige slaapklachten verder doet toenemen. Of wellicht is er een gemeenschappelijke oorzaak (bijvoorbeeld roken, comorbiditeiten) voor zowel de slaapklachten als verslechtering van de longfunctie. Deze oorzaak-gevolg kwestie zou verder onderzocht moeten worden.

Omachi et al. toonden aan dat het optreden van slaapklachten bij patiënten met COPD geassocieerd is met een verhoogde mortaliteit.[5] Het is onduidelijk of slaapklachten direct verantwoordelijk zijn voor deze verhoogde mortaliteit, of dat een andere factor zowel de slaapklachten als de verhoogde mortaliteit veroorzaakt. Onderzoek is nodig om deze onduidelijkheid op te helderen.

Slaapmedicatie

Omdat slaapklachten veel voorkomen bij patiënten met COPD, kan het zijn dat ze regelmatig hun arts verzoeken om een slaapmiddel voor te schrijven. Hoewel het verleidelijk lijkt om zo'n verzoek in te willigen, dient het voorschrijven van slaapmiddelen aan patiënten met COPD met zorg te gebeuren. Slaapmedicatie kan een negatieve invloed hebben op de ademhaling tijdens de slaap, zowel bij gezonde mensen als bij patiënten met COPD **(hoofdstuk 2)**. In richtlijnen van de American Thoracic Society (ATS) en de European Respiratory Society (ERS) staat dat slaapmedicatie vermeden dient te worden bij patiënten met ernstig COPD.[6] Dit advies is gebaseerd op studies die bescheiden nadelige effecten van slaapmedicatie op de ademhaling lieten zien.[7-11] Benzodiazepines en niet-benzodiazepine benzodiazepine-receptor agonisten (NBBRAs) kunnen nadelige bijwerkingen hebben; ze verminderen de centrale gevoeligheid voor hypoxische en hypercapnische prikkels, ze kunnen de 'arousal respons' die volgt op hypoxemie en/of hypercapnie dempen en ze kunnen de bovenste luchtweg weerstand doen toenemen doordat die middelen een spierverslappend effect hebben.[7-11] Andere studies echter vonden geen nadelige effecten van benzodiazepines en NBBRAs op de ademhaling.[12-19] Jammer genoeg zijn deze elkaar tegensprekende studies moeilijk met elkaar te vergelijken en is op meerdere punten van deze studies kritiek te leveren. Zo zijn bijvoorbeeld de studie periodes erg verschillend: van enkele uren overdag tot één nacht tot meerdere opeenvolgende nachten. Daarnaast werden in sommige studies gezonde mensen bestudeerd en in andere studies patiënten met diverse mate van COPD bestudeerd, diverse benzodiazepines met verschillende farmacologische eigenschappen werden gebruikt en de respiratoire variabelen varieerden tussen de verschillende studies. Een meta-analyse is nodig om de volgende vraag te beantwoorden: wat is het effect van slaapmiddelen op de ademhaling tijdens de slaap bij patiënten met COPD? Het is tegelijkertijd duidelijk dat het verrichten van een dergelijke meta-analyse appels met peren vergelijken is door de grote diversiteit van de verrichte studies. Zo'n meta-analyse zal

waarschijnlijk geen betrouwbare uitkomsten geven. De eerdergenoemde vraag kan enkel beantwoord worden door een nieuw studie te verrichten. Een nieuwe studie zou zowel gezonde mensen als patiënten met verschillende mate van COPD moeten includeren. Daarnaast zouden meerdere slaapmiddelen met verschillende farmacologische eigenschappen met elkaar vergeleken moeten worden in één studie en de studie periode zou moeten bestaan uit meerdere opeenvolgende nachten.

De momenteel beschikbare studies geven aan dat tussen de kort- en middellang-werkende benzodiazepines en 'nieuwere' NBBRAs zoals zaleplon, zolpidem en zopiclon enkel kleine verschillen bestaan met betrekking tot de nadelige effecten op de ademhaling. De langer-werkende benzodiazepines lijken meer nadelige effecten op de ademhaling te geven **(hoofdstuk 2)**. Op basis van de huidige kennis is er geen voorkeur voor één bepaald slaapmiddel bij de behandeling van slaapklachten bij mensen met COPD. Desondanks is het verstandig om een kort- of middellang-werkend middel voor te schrijven om de kans op bijwerkingen (overdag) te minimaliseren. Het is niet verstandig om een ander medicijn dan een benzodiazepine of NBBRA te gebruiken tegen slaapklachten, omdat het gebruik van alternatieve middelen als sederende antidepressiva, antihistaminica (zoals promethazine), melatonine en 'over-the-counter'- medicijnen niet ondersteund wordt door wetenschappelijk bewijs **(hoofdstuk 2)**.

Om de behandelopties voor COPD patiënten met slaapklachten te verbeteren, is wetenschappelijk onderzoek nodig met als doel de relatie op te helderen tussen verschillende individuele factoren (zoals nachtelijke hypoxemie, inspiratoire spierkracht, cardiovasculaire comorbiditeit, longfunctie, roken, angst/depressie) en het optreden van slaapklachten bij COPD.

De effecten van door patiënten met COPD frequent gebruikte pulmonale medicatie zoals β_2-agonisten and anticholinergica op de slaapkwaliteit lijken verwaarloosbaar.[20] Steroïden per os ingenomen beïnvloeden mogelijk negatief de slaapkwaliteit,[21] maar het is onbekend of geïnhaleerde steroïden ook een negatieve invloed op de slaapkwaliteit hebben.

De mate van slaapmiddelgebruik werd onderzocht in een eerstelijnspopulatie van patiënten met COPD, patiënten met diabetes mellitus (DM) en gezonde proefpersonen **(hoofdstuk 3)**. Het gebruik van slaapmiddelen door patiënten met COPD bleek aanzienlijk te zijn (circa 20%), maar niet significant verschillend van de andere twee studiegroepen. Dus ondanks dat richtlijnen adviseren om geen slaapmiddelen voor te schrijven aan patiënten met COPD, heeft toch een aanzienlijk deel van die patiënten ooit een slaapmiddel gebruikt. Het kan zijn dat artsen niet bekend zijn met de mogelijk schadelijke bijwerkingen van benzodiazepines, of dat artsen de ATS/ERS richtlijnen negeren, mogelijk omdat de patiënten met COPD zoveel last hebben van hun slaapklachten. Meer studies zijn nodig om deze aannames over voorschrijfgedrag en

–motivatie van artsen te onderzoeken en om alternatieve behandelopties voor slaapklachten bij deze patiënten te ontwikkelen c.q. verbeteren.

De benzodiazepine temazepam was het slaapmiddel dat het meest frequent werd voorgeschreven, gevolgd door oxazepam en diazepam **(hoofdstuk 3)**. Er waren geen verschillen tussen de studiegroepen qua voorgeschreven slaapmiddelen.

Omdat a. het totale gebruik van slaapmiddelen bij patiënten met COPD aanzienlijk is, b. deze middelen negatieve invloeden op de ademhaling kunnen hebben en c. een slechte slaapkwaliteit de kwaliteit van leven nadelig beïnvloedt, zouden artsen speciale aandacht moeten besteden aan de slaapklachten van patiënten met COPD. Daarnaast is het verstandig om eerst een niet-farmacologisch behandeling toe te passen en pas bij falen van deze behandeling een slaapmiddel voor te schrijven.

Temazepam

Het herhaaldelijk gebruik van temazepam beïnvloedt niet de ademhaling en gaswisseling tijdens de slaap bij patiënten met ernstig COPD die slaapklachten hebben **(hoofdstuk 5)**. Daarnaast heeft temazepam geen positieve of negatieve effecten op de ademhaling overdag, de gaswisseling en dyspnoe overdag bij deze patiënten **(hoofdstuk 5)**.

Onze bevindingen suggereren dat temazepam veilig kan worden gebruikt door patiënten met COPD zonder nadelige effecten op de ademhaling. Dit is een belangrijke bevinding, want het verschaft patiënten en artsen een behandelmogelijkheid tegen slaapklachten zonder dat ze zich zorgen hoeven te maken over ongunstige bijwerkingen op de ademhaling. Desalniettemin moeten artsen zich nog wel bewust zijn van andere bijwerkingen van temazepam en het advies om het middel niet langer dan een maand achtereenvolgend te gebruiken.[22]

Een studie uit 2009[23] liet zien dat ramelteon (een melatonine receptor agonist) ook veilig te gebruiken is door patiënten met matig tot ernstig COPD. Echter, in die studie werd ramelteon maar één nacht gebruikt, de transcutane PCO_2 werd niet gemeten tijdens de slaap (de zuurstofsaturatie (SpO_2) werd gebruikt als primair eindpunt) en het was onduidelijk of de polysomnografieën in die studie handmatig waren geanalyseerd.

De bevindingen in hoofdstuk 5 zorgen er niet meteen voor dat de richtlijnen over het gebruik van slaapmiddelen bij patiënten met COPD aangepast moeten worden. Een zwakte van de studie in hoofdstuk 5 is namelijk het aantal geïncludeerde proefpersonen. Alhoewel het aantal proefpersonen voldoende was om de statistisch significante conclusie te trekken dat temazepam veilig is voor patiënten met COPD als geheel, het zou kunnen zijn dat op individueel niveau nadelige effecten toch optreden. Sommige patiënten zouden meer gevoelig kunnen zijn voor de nadelige bijwerkingen van temazepam dan andere patiënten. Daarom is de studie in hoofdstuk 5 een oriënterende studie en kunnen richtlijnen pas aangepast worden nadat grotere

studies met grotere studiepopulaties verricht zijn, zodat de effecten van temazepam op de ademhaling ook bij de eventueel 'meer gevoelige' patiënten onderzocht zijn. Wellicht kan een nog te maken vragenlijst die 'meer gevoelige' patiënten aanwijzen. Dit dient nader onderzocht te worden. Het zou bijvoorbeeld kunnen zijn dat patiënten met COPD die meer kans hebben op het ontwikkelen van hypoxemie, ook degenen zijn die meer kans hebben op ongunstige effecten van temazepam. Vos et al. beschreven patiënten met COPD die meer kans hadden op nachtelijke hypoxemie. Onderzoek moet verricht worden naar de risicofactoren voor het ontwikkelen van nadelige effecten op de ademhaling door benzodiazepine-gebruik bij gezonde mensen en bij patiënten met COPD.

Artsen moeten beseffen dat de bevindingen in hoofdstuk 5 niet gelden voor andere, gerelateerde situaties zoals het gebruik van andere benzodiazepines, hogere doses van temazepam, patiënten met een exacerbatie van hun COPD, hypercapnisch COPD of patiënten met COPD in combinatie met een slaapapnoesyndroom of een andere longaandoening. Zo worden benzodiazepines niet alleen gebruikt om de slaap te bevorderen; ze worden soms ook voorgeschreven voor andere indicaties, bijvoorbeeld ter bestrijding van angst. Voor deze indicatie worden vaak langer-werkende benzodiazepines zoals oxazepam gebruikt. Het blijft onduidelijk of deze benzodiazepines veilig kunnen worden gebruikt bij patiënten met COPD.

Meer onderzoek zou verricht moeten worden naar de veiligheid van temazepam en andere benzodiazepines en NBBRAs bij patiënten met COPD en de bovengenoemde situaties. Totdat dergelijke studies verricht zijn dient temazepam behoedzaam voorgeschreven te worden aan mensen met COPD en enkel nadat niet-farmacologische behandelingen gefaald hebben.

Toekomstige studies op het gebied van slaapklachten bij patiënten met COPD zouden met name gericht moeten zijn op de ontwikkeling en verbetering van andere, niet-farmacologische behandelingen voor slaapklachten. Tot op heden heeft maar één studie cognitieve gedragstherapie voor de behandeling van slaapklachten onderzocht bij patiënten met COPD.[25] Die studie toonde dat cognitieve gedragstherapie de slaapkwaliteit bij patiënten met COPD verbeterde. Echter, die studie had een te kleine studiepopulatie en onderzocht enkel de korte termijn effecten van de therapie. De studie toonde wel dat cognitieve gedragstherapie een veelbelovende behandeling is, maar die behandeling moet nog verder onderzocht worden.
Alvorens slaapmedicatie te starten dient de eerste stap in de behandeling van slaapklachten bij patiënten met COPD het optimaliseren van de reguliere COPD-behandeling te zijn en aan patiënten te adviseren het roken te staken. De incidentie van slaapproblemen bij patiënten met COPD is namelijk positief gerelateerd aan de mate van respiratoire klachten en roken (maar zoals eerder al genoemd is er geen oorzakelijk verband gevonden).[20]

Koolstofdioxide

De overeenkomst tussen arterieel en transcutaan gemeten koolstofdioxide (respectievelijk $PaCO_2$ en $PtcCO_2$) tijdens een cardiorespiratoire inspanningstest, zoals gemeten met de gebruikte sensor, is klinisch acceptabel **(hoofdstuk 4)**. Recent zijn enkele studies gepubliceerd die het gebruik van de sensor in andere situaties, zoals tijdens non-invasieve ventilatie[26,27] en op de spoedeisende hulp,[28] onderzochten. De prestaties van de transcutane sensor zijn niet onderzocht tijdens de slaap. Dit komt door een praktisch probleem bij het uitvoeren van een dergelijke studie; waarschijnlijk zouden de proefpersonen niet doorslapen als een arteriële punctie zou worden verricht of als bloed uit een arteriële lijn zou worden afgenomen. Daarom werd bij de studie in hoofdstuk 4 gekozen voor een situatie die uitstekend geschikt was voor het vergelijking van de $PaCO_2$ en $PtcCO_2$ met elkaar: een cardiopulmonale inspanningstest. En omdat bleek de sensor nauwkeurige metingen verricht bij proefpersonen die in een instabiele cardiorespiratoire situatie zijn zoals tijdens een inspanningstest, is het waarschijnlijk dat diezelfde sensor goed functioneert als (proef-) personen in een meer stabiele situatie zijn zoals tijdens de slaap. Andere studies bestudeerden de prestaties van de transcutane sensor gedurende een lang aaneengesloten tijd; de sensor gaf nauwkeurige metingen bij intensive care-patiënten.[29,30] Het is aannemelijk dat de transcutane sensor even goed presteert bij proefpersonen die slapen als bij patiënten op een intensive care, omdat de situatie tijdens de slaap (houding, mate van bewustzijn, duur van de metingen) vergelijkbaar zijn met de situatie bij een intensive care-patiënt. De mogelijkheid om betrouwbaar de PCO_2 te meten tijdens de slaap is een belangrijke verbetering bij het beoordelen van de respiratoire functie tijdens de slaap, omdat de PCO_2 sterk correleert met de kwaliteit van de ventilatie. De bevindingen in hoofdstuk 4 zorgen voor een betere methode om de ventilatie te beoordelen tijdens slaap dan de methodes die in eerdere studies gebruikt werden.

Polysomnografie

We onderzochten de overeenstemming tussen de geautomatiseerde analyse van polysomnografieën (PSG's) en handmatige analyse van PSG's (de gouden standaard) **(hoofdstuk 6)**. Men dacht dat de vooruitgang in elektronica en techniek voor middelen zouden zorgen die de last van het handmatig analyseren van PSG-data overbodig zou maken. Die 'last' bestaat uit het tijdrovende en arbeidsintensieve werk om de grote hoeveelheid data die tijdens een PSG wordt verzameld te analyseren.

De overeenstemming van geautomatiseerde analyse van PSG's van mensen met (en ook van mensen zonder) COPD met handmatige analyse is slecht **(hoofdstuk 6)**. De overeenstemming was slecht bij zowel de slaap parameters als bij de respiratoire parameters. Dit verschil heeft gevolgen voor artsen. Zo is bijvoorbeeld een bias van 1.4 uur in totale slaaptijd is een klinisch relevant verschil. En een bias van 8.5 events per uur in de apnoe-hypopnoe-index kan tot gevolg hebben dat bij

iemand wel of niet de diagnose obstructief slaapapnoesyndroom (OSAS) gesteld wordt. Dit verschil tussen uitkomsten van handmatige en geautomatiseerde analyses komt waarschijnlijk doordat het moeilijk is voor het geautomatiseerde systeem om verschillende slaapstadia van elkaar te onderscheiden (met name REM slaap en non-REM slaap stadium 2 van non-REM slaap stadium 1), doordat het lastig is om subtiele veranderingen in de PSG-opnames te herkennen.

Eerdere studies onderzochten de overeenkomst van geautomatiseerde analyse met handmatige analyse in de volgende proefpersonen: gezonde mensen,[31] mensen die mogelijk leden aan een vorm van gestoorde ademhaling tijdens de slaap,[32,33] depressieve patiënten en patiënten met insomnia[34] en kinderen.[35] Sommige van deze studies vonden een goede overeenkomst tussen handmatige en automatische analyse,[31,34,36-38] terwijl andere studies die niet vonden.[32,33,35,39-41] Deze discrepanties in gevonden overeenkomst laten zien dat het niet vanzelfsprekend is om automatische analyses van PSG's te gebruiken bij wetenschappelijk onderzoek en in de medische praktijk. De precisie van automatische analyses zou onderzocht moeten worden in elke patiëntengroep waarvan bekend is dat hun slaap gestoord kan is, zoals patiënten met hartaandoeningen, depressie, hypertensie, eindstadium nierinsufficiëntie, DM, maagzweren, artritis, migraine en andere neurologische aandoeningen, astma bronchiale, COPD en menstruatie-problemen.[42] Het is zorgwekkend dat een geautomatiseerd systeem voor PSG-analyse gebruikt kan zijn bij verschillende studies, zoals bijvoorbeeld een studie die hierboven besproken werd.[23] De meeste studies, maar niet alle, vermeldden hoe de PSG-data geanalyseerd zijn. Om onduidelijkheid te voorkomen zouden alle toekomstige artikelen dit moeten vermelden.

Misschien dat automatische analyse toch gebruikt kan worden; niet als een complete vervanging van de handmatige analyse, maar als een aanvulling. In enkele studies[38,43,44] werd een semi-automatisch systeem gebruikt bij de analyses: de PSG-data werden initieel 'voorbewerkt' door een automatisch systeem, waarna iemand handmatig deze voorbewerkte data verder analyseerde. Of er een rol is weggelegd voor automatische analyse van PSG's dient onderzocht te worden als verbeterde automatische systemen beschikbaar zijn gekomen.

Aanbevelingen

De niet-farmacologische behandelopties voor slaapklachten bij patiënten met COPD dienen verbeterd te worden. Eén van deze behandelopties is bijvoorbeeld cognitieve gedragstherapie. De rol van cognitieve gedragstherapie bij de behandeling van slaapklachten bij patiënten met COPD moet nader worden bestudeerd. Verder zouden artsen goed bekend moeten zijn met het belang van slaaphygiëne. Ze zouden adviezen over een goede slaaphygiëne moeten geven aan patiënten met COPD met slaapklachten, alvorens te starten met slaapmedicatie.

Meer studies zouden gedaan moeten worden om te achterhalen wat de risicofactoren zijn voor mensen met COPD om slaap klachten te krijgen en wat de risicofactoren zijn voor het ontwikkelen van nadelige effecten op de ademhaling door benzodiazepines. De resultaten van hoofdstuk 5 moeten bevestigd worden in een studie met een grotere studiepopulatie, zodat eventuele 'meer gevoelig voor temazepam'-patiënten met COPD ook geïncludeerd worden, met patiënten met verschillende ernst van hun COPD en mensen zonder COPD, waarbij diverse slaapmiddelen met verschillende farmacologische eigenschappen met elkaar worden vergeleken, en met een studieperiode van meerdere aaneengesloten nachten. Alleen na het verrichten van een dergelijke studie kunnen richtlijnen over het gebruik van slaapmiddelen bij COPD aangepast worden.

Studies zouden verricht moeten worden om de veiligheid van temazepam en andere benzodiazepines en NBBRAs te onderzoeken bij patiënten met een exacerbatie van hun COPD, bij hypercapnische patiënten, bij patiënten met COPD in combinatie met een slaapapnoesyndroom en bij patiënten met een andere longziekte dan COPD.

Tenslotte, de slaapkwaliteit van patiënten met COPD kan ernstig verstoord zijn en artsen zouden speciale aandacht moeten besteden aan de slaapklachten bij deze patiënten, omdat een verbeterde slaapkwaliteit een gunstige invloed zal hebben op de kwaliteit van leven van patiënten met COPD met slaapklachten. Behandelopties voor deze slaapklachten zijn niet alleen niet-farmacologisch, maar de benzodiazepine temazepam kan veilig gebruikt worden om de slaap te bevorderen zonder enige nadelige effecten op de ademhaling.

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List of publications

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Stege G, Vos PJE, van den Elshout FJJ, Dekhuijzen PNR, van de Ven MJT, Heijdra YF. Sleep, hypnotics, and Chronic Obstructive Pulmonary Disease.
Respir Med 2008; 102(6): 801-14

Stege G, Kersten M, Bor H, Dekhuijzen PNR, Vos PJE, van den Elshout FJJ, van Weel C, Heijdra YF, Schermer T. The use of sleep medication in patients with COPD in primary care.
Submitted

Stege G, van den Elshout FJJ, Heijdra YF, van de Ven MJT, Dekhuijzen PNR, Vos PJE. Accuracy of transcutaneous carbon dioxide tension measurements during cardiopulmonary exercise testing. Respiration 2009; 78(2): 147-53

Stege G, Heijdra YF, van den Elshout FJJ, van de Ven MJT, de Bruijn PJ, van Sorge AA, Dekhuijzen PNR, Vos PJE. Temazepam 10mg does not affect breathing and gas exchange in patients with severe normocapnic COPD. Respir Med 2010; 104(4): 518-24

Stege G, Vos PJE, Dekhuijzen PNR, Hilkens PHE, van de Ven MJT, Heijdra YF, van den Elshout FJJ. Manual vs. automated analysis of polysomnographic recordings in patients with chronic obstructive pulmonary disease. Sleep Breath 2012, DOI: 10.1007/s11325-012-0714-2

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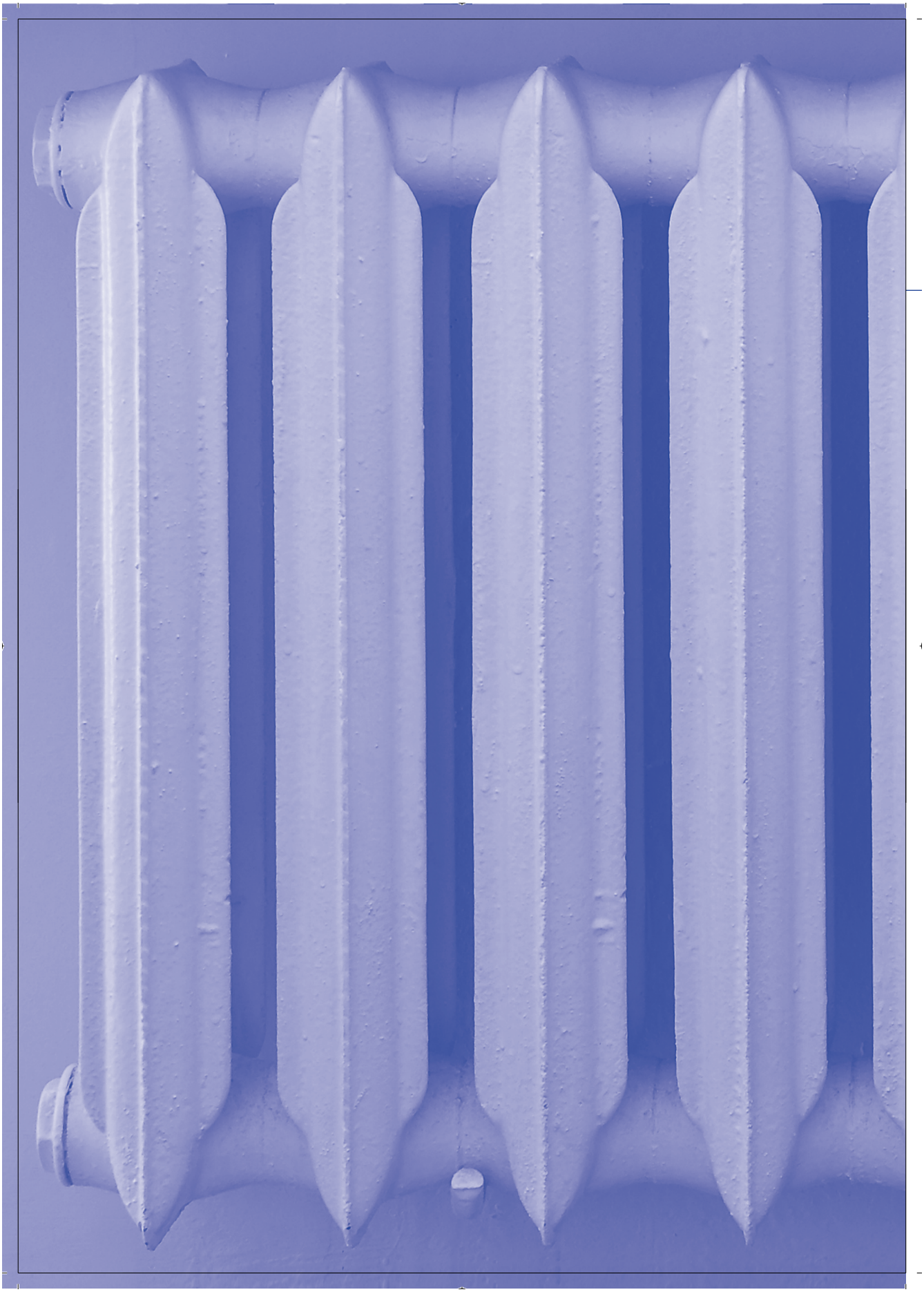

Curriculum Vitae

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Gerben Stege was born on 4 August 1977 in Warnsveld, the Netherlands. In his childhood he moved to Willemstad in Noord-Brabant, the Netherlands. From 1989 to 1995 he went to secondary school at the St. Norbertuscollege in Roosendaal. He moved to Nijmegen in 1995 to study at the medical school at the Radboud University Nijmegen Medical Centre. His medical degree was obtained in 2002. As a medical student he performed a research project in 2001 at the neonatal intensive care unit of the Royal Victoria Infirmary in Newcastle upon Tyne, United Kingdom. It was during this internship that he developed his interest for research. Thereafter he first worked at the neonatal intensive care unit in the Radboud University Nijmegen Medical Centre, followed by a job as an intern at the Department of Internal Medicine at the Rijnstate Hospital in Arnhem. In 2005 he started a PhD-program at the department of Pulmonology of the Rijnstate Hospital in Arnhem. The subject of the phD-program was the sleep and breathing during sleep in patients with chronic obstructive pulmonary disease and it resulted in this thesis.

As part of his training to become a pulmonologist, he worked as an internal resident at the Department of Internal Medicine of the Canisius Wilhelmina Hospital in Nijmegen from 2008 until 2010. Since 2010 he works as a pulmonary resident at the Department of Pulmonology of the Rijnstate Hospital in Arnhem. He lives together with Lotte and their sons Teun (6), Siem (3) and Douwe (1 year(s)).