Treatment effects of sleep apnoea: where are we now?

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ABSTRACT: The present article summarises some of the topics of discussion held during one of the workshops in preparation for the 7th International Symposium of the Katholieke Universiteit Leuven on “Respiratory somnology: a clinical update; March 2006”. Participants discussed the effectiveness of treatment in obstructive sleep apnoea/hypopnoea syndrome (OSAHS).

Of the topics discussed, the following are considered in the present article. 1) Sleepiness and attention deficit, as well as higher cognitive/executive defects in OSAHS, and the closely related clinical dilemma of “how to deal with the car-driving-ability problem in OSAHS”. 2) Continuous positive airway pressure (CPAP) in post-stroke patients. The most important data discussed during the workshop for 1) and 2) are presented in the present article. 3) The effects of CPAP on metabolic outcome. One metabolic dysfunction of OSAHS is the change in leptin and ghrelin levels, which represent the “yin and yang” of an appetite regulation system that has developed to inform the brain about the current energy balance state. Data on the impact of sleep loss, either behavioural or OSAHS-related, on this neuroendocrine regulation of appetite are also presented.

The participants ended the workshop with a discussion session on the results of more “controversial” treatment strategies for obstructive sleep apnoea/hypopnoea syndrome, such as cardiac pacing, hyoid bone expansion (a preliminary surgical technique), drug treatment for obstructive sleep apnoea/hypopnoea syndrome, female hormone replacement therapy and the role of stimulants for refractory sleepiness in already treated obstructive sleep apnoea/hypopnoea syndrome patients.

KEYWORDS: Cardiac pacing, drug treatment, insulin resistance, sleep apnoea, sleepiness, stroke

The present article is a summary of the discussion held by experts during one of the workshops in preparation for the 7th International Symposium of Katholieke Universiteit Leuven on “Respiratory somnology: a clinical update”. The participants discussed in detail the effectiveness of continuous positive airway pressure (CPAP) on different outcome parameters of obstructive sleep apnoea/hypopnoea syndrome (OSAHS), which are as follows: sleepiness and cognitive performance, cardiovascular outcome, metabolic outcome and mortality. Preliminary and/or controversial results of other treatment strategies were also discussed, including cardiac pacing, surgical hyoid expansion and hormone/drug treatment.

EFFECTS OF CPAP ON SLEEPINESS AND COGNITIVE PERFORMANCE IN OSAHS

Effects on excessive daytime sleepiness and cognitive behavioural dysfunctions

Excessive daytime sleepiness

Daytime sleepiness is the most common complaint of patients with OSAHS. At first glance, there are two mechanisms by which OSAHS may produce sleepiness [1]. 1) Breathing disturbances are accompanied by sleep arousals resulting in sleep fragmentation; and 2) hypoxaemia occurs during apnoeic events and might result in repetitive brain oxygen desaturations. The importance of these mechanisms, their link with sleepiness and the impact of CPAP treatment need to be clarified.

Arousal versus hypoxia

ROEHRS et al. [2] demonstrated that in patients with OSAHS, based on multiple regression analysis using arousal index and measures of hypoxaemia as predictors, the arousal index was the best predictor of multiple sleep latency test (MSLT) score. Their finding was supported by COLT et al. [3], who treated OSAHS patients who had sleep fragmentation and hypoxaemia at baseline with either an optimal CPAP pressure (leading to no further sleep fragmentation or hypoxaemia) or CPAP with episodic exposure to 100% nitrogen (resulting in no sleep fragmentation but regular episodes of hypoxaemia). Under
both sets of experimental conditions, mean MSLT scores were improved compared with baseline. Consequently, the authors concluded that hypoxaemia alone is not a cause of daytime sleepiness. Conversely, KINGSHOTT et al. [4] could not demonstrate any relationship between the arousal index and objective parameters of sleepiness (either the MSLT or the maintenance of wakefulness test (MWT); fig. 1). In addition, KINGSHOTT et al. [4] were unable to demonstrate any significant relationship between the apnoea/hypopnoea index (AHI) and objective parameters of sleepiness (fig. 1). The only significant relationship between nocturnal variables and objective sleepiness was a very weak correlation between the lowest oxygen saturation and the mean MWT result. CHERVIN and ALDRICH [5] demonstrated that the AHI was useful in explaining variation in measured levels of sleepiness in their study population, and that the minimum arterial oxygen saturation was as important as the AHI to the level of sleepiness.

Various CPAP interventional studies have been published. BENNETT et al. [6] found that sleep fragmentation indices are useful for identifying OSAHS patients with sleepiness who are likely to respond to CPAP. However, KINGSHOTT et al. [7] demonstrated that the baseline arousal frequency was no predictor of improvement of sleepiness after CPAP treatment. They found statistically significant relationships between measures of baseline nocturnal hypoxaemia and improvements of sleepiness; however, these correlations were weak: in no case did it explain >22% of the variance.

It is important to know why contradictory studies can be found, and why the relationships found are only weak. This might be due to the confoundingly high prevalence of excessive daytime sleepiness (EDS) in the general population. In the Sleep Heart Health Study, GOTTLES et al. [8] demonstrated that even 21% of community-dwelling subjects with an AHI <5 demonstrated an Epworth sleepiness scale score >10, compatible with subjective hypersonolence. In addition, BIXLER et al. [9], who assessed the association between EDS and sleep apnoea considering a wide range of possible risk factors for sleepiness in a population sample of 16,583 males and females, demonstrated that depression was the most significant risk factor for EDS, followed by body mass index (BMI), age, sleep duration, diabetes, smoking and, finally, sleep apnoea. However, sleep apnoea did not make a significant contribution to the model (p=0.266).

OSAHS is an inflammatory disease (a subject that will be discussed in more detail by Buyse et al. [10] in the present issue of the European Respiratory Review (ERR)); consequently the question of whether and how much inflammation contributes

**FIGURE 1.** There is no relationship between the objective multiple sleep latency test (MSLT) and the maintenance of wakefulness test (MWT) during daytime and the apnoea/hypopnoea index (a and c) or arousal index during sleep (b and d). SOL: sleep onset latency. a) rho=0.02, p=0.85; b) rho=0.12, p=0.14; c) rho=0.05, p=0.55; and d) rho=0.08, p=0.36. Reproduced from [4] with permission from the publishers.
to EDS is intriguing. The inflammatory cytokines, tumour necrosis factor (TNF-α) and interleukin (IL)-6, play a role in mediating sleepiness in disorders of EDS in humans (fig. 2) [11, 12]. TNF-α and IL-6 are elevated in patients with sleep apnoea, and this elevation is compounded with, but independent of, obesity (fig. 2) [12]. Moreover, in a pilot, placebo-controlled, double-blind study, Vontzas et al. [13] demonstrated a marked decrease in sleepiness. They prescribed etanercept (a TNF-α antagonist) in obese patients with OSAHS and demonstrated an increase of mean sleep latency on MSLT of 3.1 min, an effect about three-fold higher than the reported effects of CPAP on MSLT in patients with OSAHS in general [14].

Other cognitive behavioural dysfunction

Sleepiness and attentional capacity deficit due to sleepiness are only one aspect of cognitive behavioural dysfunction in patients with OSAHS [15]; higher cognitive/executive level deficits are also present [16–18]. Executive functions allow individuals to use their basic skills (e.g. core language skills) adaptively in a complex and changing external environment. Thus, persons of high intellect but poor executive functioning may experience occupational and social failure because their verbal discourse is disorganised, disjointed and marked by “losing track” of what was being said, and may at times be redundant, irrelevant or tangential, rigid or lacking in appropriate emotional overtones.

In 2002, a theoretical OSAHS model proposed that sleep disruption and blood gas abnormalities prevent sleep restorative processes and induce chemical and structural central nervous system cellular injuries that are linked to prefrontal system executive deficits (fig. 3) [16]. Consequently, cognitive executive system deficits in patients with OSAHS drew the attention of the research community to specific regions of the brain. Thomas et al. [19] performed magnetic resonance imaging (MRI) during executive cognitive testing before and after treatment with CPAP. Executive cognitive test results were significantly lower in OSAHS patients than in healthy subjects and the MRI showed absence of prefrontal activation. After treatment with CPAP, resolution of subjective sleepiness occurred but with no significant change in cognitive-behavioural executive performance and a persistent lack of prefrontal activation (fig. 4) [19].

Based on current scientific knowledge, it is impossible to differentiate the impact of chronic intermittent hypoxaemia from the impact of sleep fragmentation and sleep deprivation on the impairment of function in the prefrontal cortex. However, it seems that executive function deficits are not improved to the same extent by OSAHS treatment as excessive daytime sleepiness (e.g. as shown in the experiment by Thomas et al. [19]). In addition, long-term intermittent hypoxaemia has been proven to have detrimental effects on, for example, the activation of pro-inflammatory pathways and induction of apoptotic events, in the rodent brain, particularly in the regions mediating sleep–wake regulations and cognitive functions [20].

In conclusion, OSAHS results in sleepiness and attention deficits, as well as higher cognitive/executive defects related to the frontal brain. It is not clear whether these disturbances are secondary to sleep fragmentation, to long-term intermittent hypoxaemia or to both. Recent observations emphasising the importance of intermittent hypoxia resulting in pro-inflammatory pathway activation are intriguing [20], and warrant further investigation.

Effects on driving ability: a matter of weight in clinical practice

Performance impairment in OSAHS is characterised by being sleepy, with micro-sleep attacks, attention lapses and increased reaction times interfering with driving ability. There is a large body of evidence linking sleep apnoea and daytime sleepiness with an increased risk of vehicle accidents, with enough evidence to suggest that CPAP treatment can counter the accident risk [21]. This raises the question as to whether screening of drivers, and especially occupational drivers, should take place for sleep apnoea and sleepiness, in order to treat the subjects and prevent traffic accidents. The following two main aspects were discussed.

The cost-effectiveness of a screening programme

The first point to be taken into account, when discussing cost-effectiveness of a screening programme, is the fact that there are no exact data regarding the size of the risk. Studies from the USA, evaluating accidents during day- and night-time,
The generally accepted prefrontal obstructive sleep apnoea/hypopnea syndrome executive dysfunction model. Adapted from [16] with permission from the publisher.

demonstrated that sleepiness was the cause in 2.5–41.6% of accidents [22, 23]. This broad range can be explained by the application of different models for the calculation of the percentage: validity of police reports, density of road traffic, modifying factors, such as alcohol, and distractions from road traffic were considered to differing extents.

**FIGURE 3.** The generally accepted prefrontal obstructive sleep apnoea/hypopnea syndrome executive dysfunction model. Adapted from [16] with permission from the publisher.

**FIGURE 4.** Functional magnetic resonance imaging of brain activation during a working memory task in healthy subjects versus patients with obstructive sleep apnoea/hypopnea syndrome (OSAHS) before and after continuous positive airway pressure treatment. Group activation map comparing a) 10 healthy subjects, where activation is more extensive and bilateral, with b) 16 patients with OSAHS without treatment and c) 16 patients with OSAHS on treatment, where there is recovery of activation in the posterior parietal, but not the prefrontal areas. Reproduced from [19] with permission from the publisher.
The second point concerns the costs of such an exercise. The cost of testing should be balanced against the accuracy (sensitivity, specificity) of the tests used; indeed, the greater the reduction in parameters (or the more simple and cheaper the screening device), the higher the risk becomes of missing the diagnosis. In addition, treatment efficacy and effectiveness must also be considered. In order to evaluate the cost-effectiveness of a screening programme, all costs for diagnosis and treatment must be set against the costs for those missed by the programme. At the present time, data on cost-effective programmes are scarce. However, pilot studies have been started. Gurubhagavatula et al. [24] applied a two-stage approach to a large cohort of commercial drivers, which included apnoea-related symptoms combined with BMI at the first stage, and oximetry at the second; polysomnography was performed in parallel. Using optimised cut-off points, specificity was 95% and sensitivity 91%. In another pilot study, still ongoing, Moskowski [25] employed a similar design, using the ambulatory Edentrace unit, instead of oximetry, and the Sleepstrip to detect apnoeas. Results from this study [25] are presently awaited.

How should we proceed?
Both pilot studies [24, 25] focused their attention on the detection of sleep apnoea. However, although the risk of traffic accidents appears to increase with the severity of sleep apnoea, the number of respiratory events, and even the arousal index, does not accurately predict daytime vigilance impairment or the risk of a traffic accident [26]. Consequently, the question arises: should testing or screening for the presence of sleep apnoea and performance of a night test be carried out, or would it be better to test whether the subject is sleepy and perform a sleepiness or attention test during the daytime? Both sleepiness and attention tests are possible, but whether these tests can adequately predict an increased risk of a road traffic accident is unknown.

Subjective sleepiness can be minimised or underestimated by the patient; thus, objective daytime testing is required. Testing under real driving conditions is theoretically possible in OSAHS patients and appears to be the gold standard, and this is likely to be more relevant to on-road driving risks than in-laboratory testing [27]. However, such tests are impractical and very laborious.

Procedure to test sleepiness
Rather than using MSLT, which measures a variable that may not be relevant to driving fitness (MSLT tests the ability to fall asleep), the MWT (electrophysiological monitoring of the ability to maintain wakefulness) has been advocated as the best tool to evaluate the fitness to safely perform potentially dangerous tasks in sleepy patients [28]; however, such electrophysiological testing is expensive. A modified, simpler test of maintenance of wakefulness, the Oxford Sleep resistance test [29], correlates well with MWT and may be useful for routine evaluation of OSAHS patients [30].

Procedure to test attention
Several tests have been used to test attention, such as the Continuous Performance Test, which measures selective and sustained attention, and the Symbol Digit Modalities test, which measures information processing speed [18]. In addition, different driving simulators exist that generally assess reaction time and/or sustained or divided attention performance [31]. Although driving simulators do not truly simulate driving, these tools attempt to test “all” neuropsychological resources that are necessary to drive safely. Driving simulator performances in OSAHS patients are indeed lower than in control subjects, and improve with effective treatment [32–36].

However, none of the results of the daytime sleepiness tests or attention tests mentioned above, including the results on the driving simulator tests, correlate with on-road conditions or predict a given individual’s risk of having an accident [26]. The combination of several tests may yield more meaningful results than a single test [37]. Indeed, Mazzu et al. [37] demonstrated that the magnitude of sleepiness and attention deficits vary among OSAHS patients: some patients presented with specific difficulties in maintaining wakefulness in soporific situations without any other attentional abnormalities, whereas others exhibited attention difficulties only when the information was presented in a more stimulating environment.

OSAHS can be eliminated by CPAP treatment. Therefore it appears important to try to evaluate fitness to drive in OSAHS patients not only at the time of diagnosis, but also after treatment has been implemented. However, no guidelines exist concerning when re-evaluations should be performed, and the following questions arise: 1) could re-evaluation take place 1 month after treatment was started or sooner; and 2) how often should a patient be re-evaluated.

As it is not clear how driving ability should be evaluated, and as there are no guidelines stating when to evaluate and re-evaluate patients, emphasising regular CPAP use and proper sleep hygiene becomes an important aspect that should not be forgotten. The problem of poor CPAP compliance in OSAHS is well known, and depends on the following factors: 1) the severity of potential side-effects; 2) the severity of apnoea and sleepiness; and 3) on other variables, including psychological ones. For instance, in 11–28% of patients, anxiety (namely claustrophobia) prevents CPAP use and, in this setting, the merits of CPAP desensitisation become apparent [38]. Weaver et al. [39] used a self-efficacy measure for sleep apnoea—instrument (SEMSA); their findings indicated that the SEMSA has strong psychometric properties and has the potential to identify patient perceptions that may indicate those most likely not to adhere to treatment. Stepnowsky et al. [40] found that CPAP compliance was significantly associated with a measure of coping-strategy variables, especially planful problem solving and confronting coping (which refers to the effort/ability of the subject to alter a situation, suggesting some degree of risk-taking and antagonism). Consequently, encouraging patients to use coping techniques might help to improve compliance.

In conclusion, there is ample evidence that untreated OSAHS patients are at risk of traffic accidents and being unfit to drive. Therefore they should be evaluated at the time of diagnosis, after treatment initiation and during regular follow-up visits. It is not yet clear whether in-laboratory testing results truly reflect a patient’s fitness to drive and can thus be used to...
recommend that subjects who perform poorly should not drive until results normalise. This issue deserves to be carefully examined in future studies. In addition, due to (sometimes intermittent) nonadherence to CPAP and/or bad sleep hygiene, the subject can demonstrate dangerous sleepiness between the test situations proposed. Psychometric tests, which detect the patient prone to nonadherence, can be worthwhile and help patients to cope with the adjustment to use CPAP. Alternatively, the development of new sensors for cars, such as posture (seat sensors) or camera-based sensors for the detection of eye blinks, with feedback of sleepiness to the driver, could be the ultimate solution for determining fitness to drive.

EFFECTS OF CPAP ON CARDIOVASCULAR OUTCOMES IN PATIENTS WITH OSAHS

CPAP treatment in OSAHS patients might result in the reduction of blood pressure, and data on the positive effects of CPAP treatment on cardiac ischaemic disease or cardiac failure also appear quite convincing. Consequently, the present working group decided to address these issues in two supplementary articles also published in the current issue of the ERR [10, 41].

Several studies have demonstrated a very high prevalence of sleep-disordered breathing (SDB) following stroke, and have suggested that obstructive apnoea predominates [42]. Establishing whether SDB in the post-stroke period pre-dated, or was caused or worsened by the stroke is difficult. Indeed, it may not actually matter; what matters is whether the presence of OSAHS in patients with stroke has an important effect on functional outcome, recovery from stroke, and if OSAHS in stroke is amenable to intervention. Consequently, the present working group focused the discussion on the question “is it useful to treat SDB after stroke?”, and posed the following questions.

Who should be treated?

It is obvious that attempts should be made to treat the patient as soon as possible, in the acute, immediate post-stroke phase. At this time, areas of the brain are thought to be critically ischaemic, with areas in boundary zones and those supplied by terminal arteries most susceptible (the so called ischaemic penumbra); any fluctuation in cerebral blood flow or blood oxygen saturation at this time may be critical.

Who is at risk of post-stroke SDB?

The majority of studies have demonstrated that typical OSAHS-type risk factors (BMI, neck circumference, snoring and pre-stroke sleepiness) are the best predictors of post-stroke SDB [43–46]. Post-stroke SDB cannot be predicted from stroke characteristics; although there is evidence that patients with lacunar strokes demonstrate worse SDB than those with anterior circulation cortical strokes [46, 47].

Should SDB be treated?

Impact on mortality

In the study by Parra et al. [48], the number of SDB events present within 48–72 h after admission for stroke or transient ischaemic attack was a powerful predictor for the 2-yr mortality (fig. 5). In their multivariate model, only SDB (AHI, 5% risk increase per unit), age, infarct localisation with involvement of the middle cerebral artery and concomitant ischaemic disease were independent predictors of mortality.

In the study by Turkington et al. [49], patients demonstrating an \( \text{AHI} > 10 \text{ events/h}\) within 24 h of admission for acute stroke had a higher mortality rate 6 months later (fig. 5). Logistic regression analysis was used to predict mortality and confounders, such as different stroke characteristics, age, BMI, neck circumference, hypertension, diabetes and oxygen saturation indexes, were entered into the equation. Stroke severity, but also severity of upper airway collapse during sleep were independently associated with death. Using receiver operating characteristic curve analysis, the authors demonstrated that the mean length of the respiratory event most significantly associated with death was 15 s, suggesting that longer respiratory events appeared to have a greater effect.

Impact on functional outcome

Iranzo et al. [50] demonstrated that the presence of SDB during the first night after cerebral infarction is correlated with early neurological deterioration, but not with functional outcome at

**FIGURE 5.** Differences in the survival of post-stroke patients demonstrating obstructive sleep apnoea/hypopnoea syndrome (OSAHS) versus no OSAHS in the immediate, acute post-stroke period with a) \( \text{AHI} > 30 \text{ events/h}\), and b) \( \text{AHI} > 10 \text{ or} < 10 \text{ events/h}\). a) \( \text{AHI} > 30 \text{ events/h}\); b) \( \text{AHI} > 10 \text{ events/h}\); p<0.04. Reproduced from [48, 49] with permission from the publishers.
Can sleep-disordered breathing be treated?

Very few studies have evaluated the role of CPAP in the recovery of stroke patients presenting OSAHS, and most of these CPAP intervention studies started CPAP in a late post-stroke rehabilitation period. These studies (only) demonstrated improvement in depressive symptoms and well-being scores [51, 52]; however, in the study by Martinez-Garcia et al. [53], it was demonstrated that long-term CPAP treatment reduced the number of new vascular events (fig. 6). Based on their data [53], it could be calculated that the appearance of new vascular events could be avoided in one out of every four patients adequately treated with CPAP.

However, in the study by Martinez-Garcia et al. [53], only 29.4% of the patients who began CPAP in the late post-stroke rehabilitation period tolerated and still used the device 2 months later. Several other studies have shown that most patients with SDB diagnosed after stroke do not tolerate or continue to use CPAP in the long term. Patients unable to adapt to CPAP typically had less hypersomnia, fewer respiratory events and a greater number of neurological repercussions of stroke [43, 51–53]. Obviously, the problem of CPAP nontolerance might especially be present when CPAP has to be started in the immediate post-stroke phase. Indeed, a recent study [43], which aimed to implement CPAP for stroke patients with sleep apnoea in the acute phase, has reported a very low compliance and was only able to maintain four out of 34 ischaemic stroke patients on long-term domiciliary CPAP. In addition, another point should be taken into account when starting CPAP in stroke patients in the acute phase: caution must be employed as it is possible that CPAP in this population could do harm. There is some controversy regarding the impact of CPAP on cerebral blood flow velocity, and even a clear fall in cerebral blood flow velocity, associated with hypocapnia and anxiety due to breathing against positive pressure, has been described [54].

In conclusion, CPAP should theoretically be started in acute post-stroke patients with OSAHS; however, compliance is low and there might be some small deleterious effects of CPAP on the cerebral blood flow velocity, although the beneficial effects may well outweigh these negative aspects. Further studies are needed to determine a formula to improve adhesion to CPAP therapy. CPAP therapy might be easier to implement in cases where it is aimed simply at prevention of more severe upper airway collapse, possibly with lower and, therefore, better-tolerated pressures. In addition, other “simple” treatment strategies should not be forgotten. Turkington et al. [55] demonstrated higher levels of SDB when stroke patients were in the supine or near-supine position, suggesting that careful positioning of patients in the immediate period after the stroke may be important.

EFFECTS OF CPAP ON METABOLIC OUTCOMES IN PATIENTS WITH OSAHS

The first aspect of the effects of CPAP on metabolic outcomes is insulin resistance, a very important topic discussed later in the current issue of the ERR [56].

A second intriguing metabolic dysfunction of OSAHS is the change in leptin and ghrelin levels. Leptin and ghrelin represent the “yin and yang” of a regulatory system that has developed to inform the brain about the current energy balance state [57]; in addition, leptin and ghrelin levels play a role in cardiovascular physiology and pathophysiology [58]. The impact of sleep loss on this regulatory system is quite intriguing.

The impact of sleep loss due to voluntary bedtime restriction of leptin and ghrelin levels

Chronic sleep loss due to voluntary bedtime restriction is increasingly common in industrialised societies. Over the past 40 yrs, in the USA, self-reported sleep duration has decreased by nearly 2 h [59, 60]. Intriguingly, the dramatic increase in the incidence of obesity seems to have developed over the same period of time as the progressive decrease in sleep duration [61, 62].

The putative impact of recurrent sleep curtailment on the risk for obesity has only been investigated recently. In one study [63], healthy young males were submitted to sleep curtailment (six nights of 4 h in bed) versus sleep extension (six nights of 12 h in bed; fig. 7). Mean 24-h levels of the anorexigenic hormone leptin were 19% lower in the case of sleep curtailment. In a second study [64], two nights of sleep restriction to 4 h of sleep compared with two nights of 10 h in bed, under controlled conditions of caloric intake (glucose infusion at a constant rate of 5 g·kg⁻¹ of body weight every 24 h.
without other sources of calories), resulted in an 18% decrease in leptin, a 28% increase in the orexigenic hormone ghrelin, and a 23–24% increase in hunger and appetite, particularly for calorie-dense foods (33–45%) with high carbohydrate content, so-called “junk food” (fig. 8a). Importantly, these neuroendocrine changes were strongly correlated with the increase in hunger (fig. 8b). If the 23–24% increase of hunger and appetite ratings during sleep restriction translates into an increase of food intake, this would correspond to a caloric excess of ~500 kcal·day⁻¹ for a young, normal-weight sedentary adult and result in a high risk of weight gain.

Increased sympathetic activity and/or decreased parasympathetic activity are likely to be one of the pathways involved in the adverse impact of sleep loss on the neuroendocrine regulation of appetite. Six nights of 4 h in bed were indeed associated with lower levels of heart rate variability, indicating a shift towards higher sympathovagal balance (fig. 7) [63]. Since leptin release is inhibited by sympathetic activity [65], it is possible that decreased leptin levels during sleep loss result from the inhibitory effect of increased sympathetic outflow. Increased cardiac sympathovagal balance could also reflect decreased vagal activity, which could explain increased ghrelin levels, as the vagus has been demonstrated to exert a negative influence in ghrelin secretion [66].

The impact of sleep loss on appetite regulation seems to be similar under acute and chronic conditions, as both short-term laboratory studies [63, 64] and studies of habitual short sleepers show similar results: recent findings from a population study involving 1,024 subjects showed that restricted sleep duration was found to be associated with reduced leptin levels, increased ghrelin levels and elevated BMI [67, 68].

**The impact of sleep loss as a consequence of SDB**

Chronic sleep loss may also be the consequence of SDB. SDB involves sleep fragmentation; however, reduced total sleep time is also a major component of this condition [69]. Furthermore, the severity of SDB is exacerbated by restricted bedtimes [70], leading to even greater sleep loss.

Obesity is associated with an increased prevalence of SDB and it is an interesting point that patients with SDB have difficulty losing weight and are more predisposed to weight gain in
comparison with similarly obese control subjects without SDB [71, 72].

Consistent with the upregulation of ghrelin observed during short sleep in subjects without OSAHS, patients with OSAHS have higher ghrelin levels that decrease to levels only slightly higher than BMI-matched controls after only 2 days of CPAP treatment (fig. 9) [73].

In contrast, while leptin levels are reduced in short sleepers (without OSAHS), patients with OSAHS display higher leptin levels than BMI-matched controls [12, 72, 73]; CPAP partly corrects this abnormality, regardless of whether weight loss occurs (fig. 9) [73–78]. The hyperleptinaemia found in obese patients, and the even more pronounced hyperleptinaemia in obese OSAHS patients is thought to reflect leptin resistance. The mechanisms involved are not fully understood. As leptin release is inhibited by sympathetic activity through stimulation of adipocyte β-3 receptors [65], leptin levels would have been

\[ \text{FIGURE 8.} \text{ a–c) Sleep restriction (—) compared with sleep extension (-----) under controlled conditions of caloric intake (arrow: continuous glucose infusion of 5 mg·kg}^{-1}\text{·h}^{-1}\text{) results in decrease in daytime leptin (a) and increase in daytime ghrelin levels (b) accompanied by increase in hunger (c) strongly correlated with the changes in leptin/ghrelin ratio (d). d) Spearman coefficient} = 0.867, p = 0.014. \text{Reproduced from [64] with permission from the publisher.} \]

\[ \text{FIGURE 9.} \text{ a) Ghrelin and b) leptin levels in obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and the impact of continuous positive airway pressure (CPAP) treatment. a) Ghrelin levels are higher in untreated OSAHS patients (●) than in body mass index (BMI)-matched controls (■), and decrease to levels only slightly higher than BMI-matched controls after only 2 days of CPAP (○), }n=9. \text{ b) Leptin levels are higher in OSAHS patients than in controls matched for BMI, sex and menopausal status, and decrease after 6 months of CPAP use. Reproduced from [73, 74] with permission from the publishers.} \]
expected to be reduced in OSAHS patients; the reason for higher leptin levels in OSAHS patients than in BMI-matched controls is unclear. Adipocyte β-3 receptor downregulation, as a result of apnoea-induced sympathetic activation, has been proposed as one possible explanation [72]. It has also been postulated that “tissue and/or arterial oxygen tension may interfere with the feedback control of leptin secretion” [78], i.e. hypoxia resulting in raised leptin concentrations. Finally, insights into the functions of leptin suggest that elevated leptin levels may reflect an adaptive response to the pathophysiological picture associated with OSAHS, including nocturnal hypoventilation and impaired glucose metabolism [79]. Indeed, leptin has been shown to be a powerful respiratory stimulant that displays its maximum efficacy during sleep [79], as well as to abolish the increase of insulin secretion after intermittent hypoxia [80].

In conclusion, chronic sleep loss, either behavioural or disease-related, affects millions of individuals in modern society and recent studies have provided evidence in support of its deleterious impact on the neuro-endocrine regulation of appetite. In the increasingly prevalent OSAHS syndrome, a feed-forward cascade of negative events generated by sleep loss (sleep fragmentation and hypoxia) are likely to exacerbate the severity of the metabolic disturbances.

**EFFECTS OF CPAP ON THE ULTIMATE OUTCOME PARAMETER: MORTALITY**

Over recent years, several important studies appeared that focused on the effect-size of CPAP on mortality. This subject is discussed in the article by LAVIE [81] in the current issue of the ERR.

**RESULTS OF MORE “CONTROVERSIAL” TREATMENT STRATEGIES FOR OSAHS**

Finally, the results of therapeutic modalities, which appear controversial at a first glance, but do possibly have a certain therapeutic potential for the future, will be discussed.

**Cardiac pacing: still a viable treatment modality for OSAHS?**

There was considerable excitement when, in 2002, GARRIGUE et al. [82] reported that atrial overdrive pacing reduced the severity of sleep apnoea. GARRIGUE et al. [82] investigated 15 patients with implanted dual-chamber pacemakers for symptomatic bradycardia, presenting sleep apnoea (seven with obstructive and eight with central sleep apnoea), and reported a 50% reduction of the number of central as well as obstructive sleep apnoea episodes. Overdrive pacing, first improves cardiac output by increasing the heart rate during sleep and, secondly, might counteract nocturnal hyperventilation by influencing cardiac vagal or sympathetic afferent neurones; two key underlying mechanisms were postulated [83, 84], as follows.

1) A low cardiac output results in an increase of circulation time, pulmonary congestion and elevated right heart pressure. In turn, a long circulation time causes an increase of circulation time between the lung and the chemoreceptor, thereby destabilising breathing by increasing loop gain. Pulmonary congestion causes activation of pulmonary J receptors, thereby inducing hyperventilation and hypoxemia with impact on the carbon dioxide tension-apnoea threshold favouring the occurrence of central sleep apnoea. Increase of right heart pressure results in an increase in venous blood volume in the pharyngeal and neck tissues, which might decrease upper airway size [85]. Consequently, improvement of cardiac output by overdrive pacing might reduce the occurrence of central apnoeas. Moreover, depending on the anatomical propensity of the airway to collapse and/or appearance of differential activation of the various respiratory/pharyngeal muscle groups, not only central but also obstructive apnoeas can develop [86, 87]. Consequently, in theory, overdrive pacing might also result in a decrease of obstructive events.

2) Given the demonstrated efficacy of atrial overdrive pacing in preventing vagally mediated atrial arrhythmias and syncopé in some patients, GARRIGUE et al. [82] concluded that atrial pacing is itself vagolytic, although nothing in the cited literature justifies this conclusion [83]. It remains an intriguing hypothesis, however, that atrial pacing might directly influence signalling from cardiac vagal or sympathetic afferents. Although their effect on respiration is unknown, cardiac synapses do form synapses in the nucleus of the tractus solitarius [88], an important component of the medullary respiratory centre [89]. Pulmonary vagal afferents to this area inhibit inspiration, and speculation that cardiac vagal afferents also inhibit respiration presents a testable hypothesis. Cardiac sympathetic afferents may also be relevant, since norepinephrine, like serotonin, has an excitatory effect on respiratory motoneurons, including those that innervate the pharyngeal muscles [89].

Subsequently, several studies have been conducted evaluating the clinical value of cardiac pacing for the treatment of sleep apnoea in patients with predominantly obstructive or central sleep apnoea.

**Obstructive sleep apnoea**

Three studies [90–92] now exist on the effect of atrial overdrive pacing in patients with a dual-chamber pacemaker implanted for symptomatic bradycardia. In these three study populations, presenting mainly obstructive sleep apnoea, overdrive pacing did not significantly affect either the AHI or the oxygen desaturation or sleep structure/fragmentation, even after performing pacing during 1 month (table 1). In addition, two other studies that aimed to evaluate the effect of atrial overdrive pacing via an externalised pacemaker in patients with obstructive sleep apnoea, but without pacemaker indication, were unable to demonstrate any significant change of sleep (breathing) parameters (table 1) [93, 94].

In summary, the striking positive effect of atrial overdrive pacing found by GARRIGUE et al. [82] was not replicated by subsequent studies. A possible reason for this discrepancy might be differences in the patient populations investigated. While obstructive and central sleep apnoea were of equal prevalence in the study by GARRIGUE et al. [82], the ensuing investigators focused specifically on the obstructive type of the syndrome [90–94]; furthermore, the patients in the first study suffered from pronounced sinus bradycardia. Moreover, none of the studies addressed patients with (obstructive) sleep apnoea and severe lowered ejection fraction: in such patients, the potential role of respiratory control system instability related to circulatory delay and hyperventilation is greater.
than in the subjects included in these studies, available at this moment.

Central sleep apnoea

To date, two studies have investigated the influence of cardiac pacing on central sleep apnoea [95, 96]. However, these studies did not focus on atrial overdrive pacing, but on cardiac resynchronisation therapy (CRT) by atrially triggered left- or bi-ventricular pacing. Indeed, CRT may be therapeutically more effective in treating central sleep apnoea, as CRT appears to have more pronounced haemodynamic benefits than atrial overdrive pacing [97]. Both studies [95, 96] focused on patients with severely impaired left ventricular function and indication for CRT according to current guidelines (table 2). In the study by Sinha et al. [95], CRT resulted in a significant reduction of the AHI by ~75%, and similar results were observed in the study by Gabor et al. [96]: CRT significantly reduced the central apnoea events by ~50%, whereas obstructive events were not affected.

In conclusion, current data do not support cardiac pacing as an alternative therapeutic strategy for the majority of patients with OSAHS and no signs of chronic heart failure. Promising evidence exists of an improvement to central sleep apnoea by CRT therapy. However, none of the studies so far have addressed the question whether atrial overdrive pacing alone or in addition to CRT can further improve the severity of central sleep apnoea.

New surgical treatment possibilities: is hyoid expansion strategy an option?

Expansion hyoidplasty was first described in dogs by Patton et al. [98]. The investigators trisected the hyoid bone just medial to each lesser cornu; the trisected hyoid bone was then held in an expanded position by a permanent brace. The greater cornua with attached middle constrictor and hyoglossus were moved laterally, while the body of the hyoid with attached genioglossus and genioglossus shifted the base of the tongue anteriorly. Consequently, a significant decrease of closing pressure in the canine upper airway was observed (fig. 10). These results support the continued experimentation towards implementation of the expansion hyoidplasty in humans.

### TABLE 1
Short-term impact of atrial overdrive pacing (+15 beats above baseline rate, with pacemaker set on a back-up pacing of 40 beats.h⁻¹)

|                  | Garrigue et al. [82] | Pepin et al. [90] | Lüthje et al. [91] | Simantirakis et al. [92] | Unterberg et al. [93] | Krahn et al. [94] |
|------------------|----------------------|-------------------|---------------------|-------------------------|-----------------------|-------------------|
| Age yrs          | 69±9                 | 71±2              | 63±2                | 60±11                   | 61±2                  | 60±13             |
| M/F              | 11/4                 | 11/4              | 19/1                | 12/4                    | 9/1                   | 12/3              |
| BMI kg.m⁻²       | 27±1                 | 28±3              | 30±1                | 33±2                    | 33±2                  | 30                |
| LVEF %           | 54±11                | 64±13             | 49±3                | 59±4                    | 54±3                  |                   |
| ΔLVEF %          | Nocturnal heart rate beats min⁻¹ | 51±8 | 64±6 | 50±3 | 55±6 | 63±2 | 65±7 |
| Nocturnal heart rate beats min⁻¹ | 16* | 11* | 11* | 17* | 13* | 12* |
| OAI without pacing events h⁻¹ | 7±4 | 5±11 | 5±1 | 11±3 |                   |                   |
| ΔOAI with pacing events h⁻¹ | -3* | -1 |                   |                   |                   |                   |
| CAI without pacing events h⁻¹ | 12±14 | 1±1 | 2±1 | 3±1 |                   |                   |
| ΔCAI with pacing events h⁻¹ | -7* | 1 |                   |                   |                   |                   |
| AHI without pacing events h⁻¹ | 27±16 | 43±27 | 21±2 | 56 | 41±7 | 39±21 |
| ΔAHI with pacing events h⁻¹ | -16* | 7 | -3 | 0 | No change | 3 |

Data are presented as n or mean±sd, unless otherwise indicated. M: male; F: female; LVEF: left ventricular ejection fraction; Δ: change; OAI: obstructive apnoea index; CAI: central apnoea index; AHI: apnoea/hypopnoea index. *: statistically significant.

### TABLE 2
Impact of >4-month cardiac resynchronisation therapy in patients with severe cardiac failure and central sleep apnoea

|                  | Sinha et al. [95] | Gabor et al. [96] |
|------------------|-------------------|-------------------|
| Age yrs          | 65±11             | 65±14             |
| M/F              | 12/2              | 12/0              |
| BMI kg.m⁻²       | 25±3              | 29±4              |
| LVEF %           | 25±5              | 19±4              |
| ΔLVEF %          | 35±9*             | 24±8*             |
| AHI without pacing events h⁻¹ | 19±10* | 43±9 |                   |
| ΔAHI with pacing events h⁻¹ | -14* | -12 |                   |
| CSR events without pacing events h⁻¹ | 31±14 |                   |
| ΔCSR events with pacing events h⁻¹ | -16* |                   |
| OAH without pacing events h⁻¹ | 10±12 |                   |
| ΔOAH with pacing events h⁻¹ | 2 |                   |

Data are presented as n or mean±sd, unless otherwise indicated. M: male; F: female; BMI: body mass index; LVEF: left ventricular ejection fraction; Δ: change; AHI: apnoea/hypopnoea index; CSR events: repetitive episodes of central apnoea or hypopnoea, with a characteristic crescendo–decrescendo pattern; OAH: obstructive apnoea/hypopnoea index. *: statistically significant; #: all patients demonstrated central sleep apnoea on polygraphy.
Recently, surgeons of the University Clinics of Antwerp (Belgium) and Mannheim (Germany) performed a human pilot study on expansion hyoidoplasty. They simplified the surgical technique used by Patton et al. [98]: the hyoid bone was split into two parts and a titanium implant (Air Frame™ system; Aspire Medical, Palo Alto, CA, USA) was attached to both split parts of the hyoid bone and screwed together in such a way that 9–11 mm lateral expansion was reached (fig. 10). Theoretically, by broadening the hyoid bone, the hypopharyngeal space enlarges and should stabilise [99].

The primary aim of this pilot study was to evaluate the safety and efficacy of hyoid expansion in a group of 17 selected patients with OSAHS presenting a clear hypopharyngeal wall collapse on sleep endoscopy [100]. The study comprised 15 males and two females, with a mean (range) age of 45 (29–54) yrs, BMI 26 (22–30) kg·m⁻² and AHI 28 (20–48) events·h⁻¹. All patients underwent pre- and post-operative sleep endoscopy under induced sleep [100], polysomnography, MRI and a three-dimensional computed tomography (CT) scan. Hyoid expansion appeared to be feasible and safe: all procedures were completed without complications or unforeseen difficulties and patients could be discharged after 3 days in good general health. However, even in this study population consisting of selected patients with a clear hypopharyngeal/lateral collapse on sleep endoscopy, the overall result on AHI, and three-dimensional CT and MRI measurement of change of upper airway size were not significant. Nonetheless, there were three responders, and further exploration is warranted.

Is there a place for medication in patients with OSAHS?
CPAP is usually effective in the treatment of OSAHS, but some people cannot tolerate it and many would prefer to take medication. A variety of drugs has been proposed, but until now, most drugs have proved to be ineffective [101]. However, some areas of pharmacological intervention still hold some promise of broader utility.

Is there a role for manipulation of the serotonergic or cholinergic systems?

What is the potential of medication influencing the serotonergic system?
The hypoglossal nerve, which is depolarised by serotonin (5-hydroxytryptamine; 5-HT), innervates the genioglossal muscle (GG), the major upper airway dilator muscle [102]. Serotonergic input from the medullary raphe to the hypoglossal motoneurons decreases from wakefulness to non-rapid eye movement (REM), to a minimum in REM sleep (fig. 11) [103]; this parallels the increase of OSAHS from non-REM to REM sleep, present in many patients.

The pharmacology of 5-HT modulation of upper airway dilator motoneurons is very complex. The following factors add to the complexity: 1) several 5-HT receptor subtypes exist; 2) 5-HT excitation not only enhances oropharyngeal opening but, in the case of excitation of some 5-HT subtypes, there is also an inhibitory hypoglossal action, presumably through autoregulatory mechanisms acting at pre-synaptic receptors; 3) moreover, 5-HT receptors are not only present in the hypoglossal motoneuron, but also elsewhere in the brain and brainstem, with possible influences on sleep generation and respiration well beyond the upper airway motoneuron activity: 5-HT affects, amongst other things, respiratory rate, and inspiratory...
and expiratory neurons; and 4) 5-HT receptors are not only present in the brain, but also in the myocardium, urinary bladder, adrenal glands, and nodose ganglion, a source of possible “adverse” events [101, 104–106].

Studies on 5-HT medication in human beings aiming to reduce pharyngeal collapse are limited and, at a first glance, disappointing.

One of the oldest 5-HT medications used is protriptyline. Protriptyline is a tricyclic antidepressant that also reduces re-uptake of 5-HT in the brain. The drug reduces REM sleep and, in a cat model, preferentially activates the hypoglossal nerve [107]. However, in humans, three randomised controlled trials (RCTs) did not find a reduction in apnoea frequency overnight [108–110].

It has also been demonstrated that the selective serotonin re-uptake inhibitor (SSRI) paroxetine increases GG activity in awake healthy volunteers [111]. However, during sleep, and in particular REM sleep, the serotoninergic medullary raphe nuclei are less active than during wakefulness and lower levels of 5-HT are released; consequently, inhibiting re-uptake will be less likely to have any affect on airway tone. Indeed, in OSAHS patients, according to the only study performed to date [112], paroxetine showed only a modest improvement of the apnoea frequency with a fall from 25–18 events h⁻¹ without any reduction of symptoms. Fluoxetine (another SSRIs) has been compared to protriptyline, and was better tolerated, but no more effective [113].

Excitation of some 5-HT subtype receptors results in a decrease rather than increase of the GG activity [105]. It is possible that, by blocking this action, the 5-HT antagonist (and anti-emetic) ondansetron decreases the frequency of apnoeas in adult bulldogs [114]. However, no effect was seen in humans, possibly because the dose of ondansetron used in the study was too low, or perhaps because the mechanism of apnoeas is different in bulldogs [115].

However, promising publications still exist, especially on the drug mirtazapine, another antidepressant that has been shown to improve sleep quality (in contrast to the other SSRIs that are associated with reduced sleep efficiency and increased arousals from sleep) [116]. Mirtazapine is an agonist at the 5-HT₃ receptor, and antagonist at 5-HT₂ and 5-HT₃ receptors [116, 117]. The drug is promising, on a theoretical basis for the following reasons. 1) Current theories of sleep apnoea pathogenesis suggest a vicious cycle between apnoea and arousal, with each behaviour perpetuating the other [118]. The cycle may be broken by blocking either apnoea or arousal. 2) A 5-HT agonist offers the possibility of affecting airway tone in sleep by raising 5-HT levels, even if the resting tone is low (as is the case during sleep). 3) 5-HT₂ and 5-HT₃ antagonistic effects appear to be a positive point: systemic injection of serotonin in rats has shown to produce apnoea, an effect mediated by 5-HT₃ and 5-HT₄ receptors in or on the nodose ganglia [119]; moreover, administration of mirtazapine (possessing both 5-HT₃ and 5-HT₄ antagonistic potential) in the rat significantly reduced central apnoea [120].

However, the implications for the management of OSAHS must be verified by appropriate clinical trials in humans. There exists one RCT on mirtazapine in OSAHS in which carley et al. [121] demonstrated that the drug significantly reduced the apnoea severity compared with placebo: a reduction of ~50% in AHI. However, this RCT only included a small number of patients (12 in total) and their promising result has not been corroborated by other larger RCTs until now. Nevertheless, a case report exists describing a male subject unable to tolerate CPAP who was treated with mirtazapine for 3 months; a fall of AHI from 40.4–9.3 events h⁻¹ was observed, with a subjective improvement in daytime sleepiness [122].

What is the potential of medication influencing the cholinergic system?

Recent work in rats has shown that cholinergic agonists directly applied to the hypoglossal motoneurone decrease tone in the GG [123]. The suppression is muscarinic and outweighs an excitatory nicotinic drive (fig. 11).

In human beings, tricyclic antidepressants and to a lesser extent SSRIs, in particular paroxetine, have anti-muscarinic activity; however, to date, this action has not been shown to be beneficial [107–110, 112].

Nicotine not only has a direct stimulating action on the hypoglossal motoneuron output: the molecule also increases ventilatory drive via respiratory neurons in the medulla [123, 124]. In a small study of patients with OSAHS, nicotine gum was given at bedtime [125]. In view of the short half-life of nicotine, gothe et al. [125] analysed the beginning of the night separately and found a reduction in AHI from 85–49 in the first hour. In a RCT, nonsmoking snorers were given transdermal nicotine at night [126]. Snoring intensity was reduced, but the number of apnoeas was not reduced and sleep quality deteriorated.

Inhibition of anticholinesterase by physostigmine, an anticholinesterase that increases both muscarinic and nicotinic activity, has been shown to elevate brain and peripheral acetylcholine content in humans with Alzheimer’s disease [127]. In an RCT, physostigmine was administered intravenously overnight to a group of patients with OSAHS [128]. The AHI was reduced by 23% compared with placebo (AHI 41 versus 54). The greatest fall in AHI was even present in REM sleep (AHI 30 versus 54). However, only one-half of subjects could be considered as responders and found that non-responders had a higher weight and that their sleep tended to deteriorate when on medication. heinzer et al. [128] suggested the following possible mechanisms for the reduction in AHI: 1) effects on ventilatory drive, as acetylcholine transmission is involved in the central regulatory control of respiration in the medulla oblongata [129, 130] as well as in chemosensory signalling in the carotid body [131]; 2) increased salivation changing airway mechanics by altering upper airway surface tension and thereby increasing airway stability [132, 133]; and 3) increased heart rate reducing the loop gain in the ventilatory control [134].

In conclusion, regarding the accumulated data, paroxetine may have a role in a minority of patients while protriptyline and ondansetron have no place in the treatment of OSAHS. The role of mirtazapine is not clear and use of this drug is associated with weight gain - a negative side-effect, especially in patients with OSAHS. Cholinergic drugs remain of interest, with benefits shown in REM sleep when OSAHS may be most
pronounced; SSRIs are least effective. The observation that different drugs have benefits in different sleep stages (non-REM versus REM) may indicate that future consideration should be given to studying drug combinations.

What is the role of oestrogen and/or progestin hormone therapy for OSAHS in post-menopausal females? Female hormones are thought to protect from SDB Community-based studies show increased prevalence of sleep apnoea after the menopause and demonstrate that an increased AHI is rare in pre-menopausal females (in the pre-menopausal females, the presence of OSAHS appeared to be associated exclusively with severe obesity) [135–137]. Consequently, one can expect that hormone therapy is able to reduce apnoea severity in post-menopausal females.

Different mechanisms to explain how female hormones protect from SDB have been postulated, as follows. 1) GAMBACCIANNI et al. [138] demonstrated that the menopause is associated with an accelerated increase of body weight and body fat, with a prevalent central, android distribution predisposing to obstructive sleep apnoea; this fat redistribution could be counteracted, at least in part, by hormone therapy. 2) Progesterone could exert its beneficial effects by increasing GG muscle tone. POPOVIC et al. [139] demonstrated that GG activity during wakefulness was highest in the luteal phase of the menstrual cycle, followed by the follicular phase, and was lowest in post-menopausal females. There was a positive correlation between progesterone levels and the GG-electro- myogram (EMG) and a significant increase of EMG activity was found in the post-menopausal females re-studied after hormone therapy. 3) Progesterone is also a respiratory stimulant; it is well known that females experience increased ventilatory drive during the late luteal phase of the menstrual cycle when progesterone is increased, as well as during pregnancy. In contrast, it has been shown that oophorectomy, with subsequent sex-steroid deficiency, is associated with decreased hypoxic ventilatory response [140]. The role of oestrogen in the control of breathing is not that clear, although it has been suggested that oestrogen may work in a synergistic

![FIGURE 12. End-tidal carbon dioxide tension (PET,CO2), PET,CO2 apnoeic thresholds (PET,CO2-AT) and differences between baseline PET,CO2 and the PET,CO2-AT (ΔPET,CO2-AT) in pre- and post-menopausal females compared with post-menopausal females and males. a) There was no significant difference in the PET,CO2-AT between groups. b) ΔPET,CO2-AT was increased in pre-menopausal females compared with both post-menopausal females and males, with no difference between the latter two groups. Comparison of c) PET,CO2, d) PET,CO2-AT, and e) ΔPET,CO2-AT at baseline and after 1 month of hormone replacement therapy (HRT) in post-menopausal females showed that PET,CO2-AT was significantly decreased and ΔPET,CO2-AT significantly increased with HRT treatment. *: PET,CO2-AT was significantly decreased and ΔPET,CO2-AT significantly increased with HRT. #: p<0.05. 1 mmHg = 0.133 kPa. Reproduced from [148] with permission from the publisher.](image-url)
manner because it increases the sensitivity for progesterone by inducing the formation of progesterone receptors [141–144]. Declining levels of these hormones might predispose some females to SDB, especially by lowering the ventilatory drive to the upper airway, which could lead to imbalance between forces with impact on upper airway patency and counteracting forces.  

4) It has been demonstrated that pre-menopausal females are less susceptible than males to the development of hypocapnic central apnoea during non-REM sleep, an observation suggesting that males have a more robust ventilatory response to arousal [145–147]; in addition, the change in end-tidal carbon dioxide tension ($P_{ET, CO_2}$) necessary to induce a central apnoea differs between pre- and post-menopausal females, and could be influenced by hormone therapy (fig. 12) [148].

Can female hormone replacement therapy be used to protect from SDB, and what can be learnt from interventional studies? The available interventional studies using polysomnography as diagnostic tool are represented in table 3. The results of all these pilot studies [149–158] are controversial. However, these studies demonstrate many of methodological limitations, as follows: a control group is often lacking; nonblinded assignment; short duration of treatment; and, especially, a very small sample size. Fortunately, the issue of the possible impact of hormone therapy on SDB has also been examined in large observational studies [135, 137], and their data are more promising. Substantial support for a role of hormone therapy has been

| First author [ref.] | Study design | Subjects n | Type of HRT | Duration of HRT | Significant impact on number of SDB events |
|---------------------|--------------|------------|-------------|----------------|------------------------------------------|
| Block [149]         | Randomised, double-blind, placebo-controlled, parallel | 11 on treatment, 10 on placebo | Progestin | 10 weeks | No (only six out of 11 had SDB at baseline); Decrease in maximum duration of apnoea |
| Pickett [150]       | Randomised, single-blind, placebo-controlled, crossover | 9 | Progestin+oestrogen | 1 week | Yes |
| Cistulli [151]      | Open-label, two arms | 6 on oestrogen | Oestrogen | 50 days | No (significant but clinically irrelevant decrease of AHI during REM) |
|                     |              | 9 on progestin+oestrogen | Progestin+oestrogen |          | HVR increase, HCVR unchanged |
| Collop [152]        | Randomised, double-blind, placebo-controlled, crossover | 8 | Progestin | 1 week | Yes; Oxygen saturation increase |
| Keele [153]         | Open label | 5 | Oestrogen Followed by progestin+oestrogen | 3–4 weeks | 25% reduction in oestrogen group; 50% in combined therapy group |
|                     |              |          |          | 12 days | Yes |
| Manber [154]        | Open label | 6 | Oestrogen + placebo during 6–13 days Followed by progestin+oestrogen during 6–13 days | 6–13 days | Oestrogen: reduced AHI (effect size 0.5) |
|                     |              |          |          | 6–13 days | Yes |
| Wesström [155]      | Open label | 5 | Progestin+oestrogen | 5–6 weeks | Yes (75% reduction in AHI) |
| Saaresranta [156]   | Open label | 10 | Progestin | 14 days | AHI unchanged (low value at baseline); IRR pattern unchanged |
| Polo-Kantola [157]  | Randomised, double-blind, placebo-controlled, crossover | 62 | Oestrogen | 3 months | Decrease in mean $P_{ET, CO_2}$ over the night |
| Saaresranta [158]   | Open label | 8 | Progestin | 14 days | Inspiratory flow; shapes less flow-limited |

SDB: sleep-disordered breathing; AHI: apnoea/hypopnoea index; REM: rapid eye movement; HVR: hypoxic ventilatory response; HCVR: hypercapnic ventilatory response; IRR: increased respiratory resistance pattern; $P_{ET, CO_2}$: end-tidal carbon dioxide pressure.
provided by the population-based epidemiology study by IXLER et al. [135]: the prevalence of sleep apnoea in post-menopausal females without hormone therapy (2.7%) was almost similar to males (3.9%), whereas in post-menopausal hormone therapy-users, the prevalence of sleep apnoea (0.5%) was compatible with that in pre-menopausal females (0.6%) [135]. In the study by SHAHAR et al. [137], the prevalence of sleep apnoea in post-menopausal females was higher than in the study by IXLER et al. [135], but, again, the prevalence in post-menopausal females on hormone therapy was 2–3 times lower than in nonusers. The power of the study by SHAHAR et al. [137] is that they performed a multivariable adjustment for known determinants of obstructive sleep apnoea, including age, BMI and neck circumference. The adjustment attenuated the inverse association between hormone use and SDB, but only moderately.

However, when considering hormone therapy, the increased risk for thromboembolic events should be noted in all oestrogen and/or progestin therapy and also the increased risk of breast cancer in patients receiving long-term oestrogen and progestin [159]. However, unopposed oestrogen therapy may not be linked to increased risk of breast cancer and there are no data on the risk of breast cancer when using progestin monotherapy [159].

In conclusion, although the results of experimental studies are controversial, based on epidemiological data showing lower prevalence of SDB in hormone therapy-users than in nonusers, post-menopausal hormone therapy (preferably progestin or oestrogen monotherapy) may be considered as a second-line treatment in selected patient groups (perhaps especially in post-menopausal females presenting OSAHS with obesity hypoventilation syndrome, i.e. patients with decreased respiratory drive) when risks of untreated SDB are likely to overcome those related to hormone therapy. Indeed, progesterone raises resting ventilation and augments chemosensitivity to a greater extent in patients with obesity-hypoventilation syndrome than in normal subjects or in patients with chronic obstructive pulmonary disease [160].

Stimulants in refractory sleepiness in sleep apnoea

The chief symptom of patients suffering from OSAHS is excessive daytime sleepiness. Long-term use of CPAP commonly improves or eliminates sleepiness; however, an unknown subset of patients remain somnolent, despite an appropriate compliance and efficacy of CPAP.

Possible explanations for this retention of somnolence are as follows. 1) “CPAP-induced sleep deprivation”: patients commonly sleep less after CPAP treatment than before. This can be caused by the positive impact on sleep by the CPAP resulting in a reduction of light, unstable non-REM sleep in favour of stable, restorative slow-wave and REM sleep; alternatively, one may imagine that some side-effects of CPAP (e.g. uncomfortable mask and mask leaks, nasal/oral dryness and nasal obstruction resulting in mouth leaks) would prolong nocturnal awakenings, and would make it difficult for the patient to resume sleep and lead to chronic sleep deprivation. 2) Refractory sleepiness can be due to alcohol and sedative drug abuse. 3) Sometimes depression, also a symptom of obstructive sleep apnoea, is not totally reversible on CPAP [161].

4) Additional sleep disorders can be present. The patient can demonstrate narcolepsy; aside from primary narcolepsy, secondary cases of narcolepsy have been observed in neurological conditions, including dystrophic myopathy, Parkinsonism and multiple sclerosis [162]. Periodic leg movements without restless legs can be present, a condition more frequent in aged patients that may be unmasked after relief of apnoea. The patient can suffer from hypersomnia, aside from idiopathic hypersomnia, a rare disease priming adolescents or young adults; there are several neurological conditions leading to secondary hypersomnia in middle-aged adults [162].

4) In addition, it is possible that some patients with OSAHS develop hypoxic lesions of central wake-active systems, leading to long-term CPAP-resistant secondary hypersomnia. Oxidative neural injury of wake-promoting neural groups has indeed been demonstrated in animal models of OSAHS (fig. 13) [163, 164].
Stimulants may improve refractory sleepiness. Some antidepressants, such as fluoxetine, might even have a mild alerting effect [165], making them a good choice in CPAP-treated OSAHS patients who are still depressed and somnolent. Caffeine is used by OSAHS patients at daily doses two times higher than in controls that do not decrease after CPAP treatment [166]. Caffeine blocks adenosine receptors that control sleep; these rebound after sleep deprivation [167]. However, both caffeine and antidepressants have not been specifically studied in this condition.

Modafinil is a well-studied nonamphetaminic alerting agent that was first developed in patients with narcolepsy and idiopathic hypersomnia [168–170]. Its mechanism of action is not fully understood, although modafinil-induced potentiation of norepinephrine transmission is observed in animals already co-treated with norepinephrine [171, 172], and the benefit of modafinil on alertness is largely incompletely known mechanisms (but still possible) risk of irritability, anxiety, restlessness and rare sympathetic effects, such as tachycardia, headache and increased blood pressure. It is the unique stimulant investigated in OSAHS patients using randomised, placebo-controlled, double-blind trials. It was previously shown to improve daytime sleepiness and memory in untreated OSAHS patients [173]. Later, it was shown to significantly reduce residual sleepiness in larger groups of CPAP-treated OSAHS patients [174–176], with rare nervousness and headaches, and no [175, 177] or marginal [174, 176] reduction of CPAP use and no increased blood pressure (table 4). The trial by Kingshott et al. [174], the first RCT on this topic, observed a significant improvement of the objective measure of MWT (table 4). However, the mean AH of the study sample while on CPAP treatment was 8 and the arousal index was 28. Although the mean pre-treatment AH and arousal index for this group were both 45, one may speculate that CPAP therapy in this group was suboptimal. In the following studies [175–177], subjective sleepiness as measured by the Epworth sleepiness scale and objective sleepiness determined by MSLT and MWT and quality of life, were statistically significantly improved (table 4). In addition, it has been shown that modafinil improved attention performance in these patients [178]. However, none of these studies has evaluated the safety of modafinil in OSAHS patients on a long-term basis, especially regarding the risk for hypertension and decreased CPAP use.

Clinicians sometimes consider the use of dexamphetamine or methylphenidate (second choice stimulant drugs used to treat narcolepsy, products blocking norepinephrine and dopamine re-uptake) for refractory sleepiness in OSAHS. However, the present authors could only find one study showing cases of treatment of OSAHS refractory sleepiness with dexamphetamine [179]. In addition, the potential benefit of these drugs may be limited by their frequent deleterious cardiovascular effects.

When taken during the night, γ-hydroxybutyrate (GHB; renamed sodium oxybate or Xyrem®) improves sleepiness in narcolepsy patients via incompletely known mechanisms (but
possibly night-time blockade/daytime release of dopamine, and increased restorative sleep). GHB had no clear effect on sleep apnoea in one study [180], but has not, so far, been tried in CPAP-treated OSAHS patients.

Pre-optic histamine neurones are part of an important vigilance system that modulate reactivity to novel environments [181, 182]. A new class of stimulants prolong histamine stimulation through partial blockade of pre-synaptic histamine-3 receptors (H3 receptors are present mainly in the brain, with a few in the stomach). They showed promising alerting effect in animal studies [183].

In conclusion, refractory sleepiness in patients with obstructive sleep apnoea/hypopnoea syndrome adequately treated with continuous positive airway pressure exists, yet the percentage is unknown. The mechanism of residual sleepiness is possibly oxidative injury in wake-active neurones. Symptomatic treatment with modafinil in these patients shows consistent benefit on vigilance with low adverse effects, although there is some concern about possible decrease of continuous positive airway pressure use. To date, there are no other valuable drugs; some products, such as sodium oxybate or products blocking the pre-synaptic histamine-3 receptors, appear promising and further tests are warranted.

APPENDIX

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B. BUYSE ET AL.

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