Eur Respir Rev 2007; 16: 106, 146–168
DOI: 10.1183/09059180.00010605

Treatment effects of sleep apnoea: where are we now?

B. Buyse* and the participants of working group 2#

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 regulatoion 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

AFFILIATIONS
*Dept of Pulmonology, Centre for Sleep Monitoring and Home Ventilation, University Hospital Gasthuisberg Leuven, Belgium.
#Participants of working group 2 are listed in the Appendix.

CORRESPONDENCE
B. Buyse
Dept of Pulmonology
University Hospital Gasthuisberg
Herestraat 49
3000 Leuven, Belgium.
Fax: 32 16346803
E-mail: Bertien.Buyse@uz.kuleuven.ac.be

STATEMENT OF INTEREST
See Appendix

The present article is a summary of the discussion held by experts during one of the workshops in preparation of 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

European Respiratory Review
Print ISSN 0905-9180
Online ISSN 1600-0617

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, GOTTLIEB *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 hypersomnolence. 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

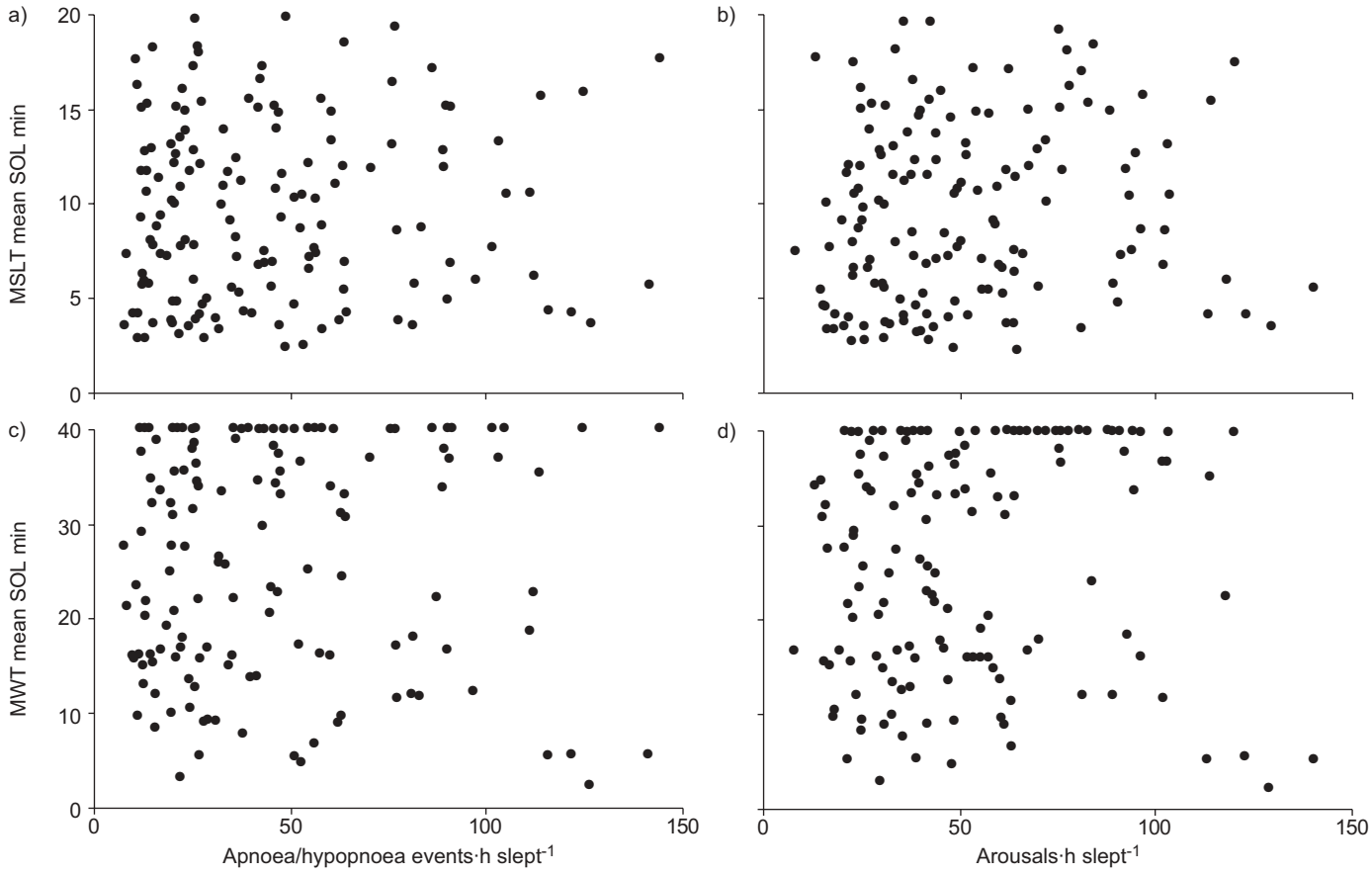

FIGURE 1. There is no relationship between the objective multiple sleep latency test (MSLT) and the maintenance of wakefulness test (MWT) during daytime and the apnoea/hypopnoea index (a and c) or arousal index during sleep (b and d). SOL: sleep onset latency. a) rho=0.02, p=0.85; b) rho=0.12; p=0.14; 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, VGONTZAS *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.

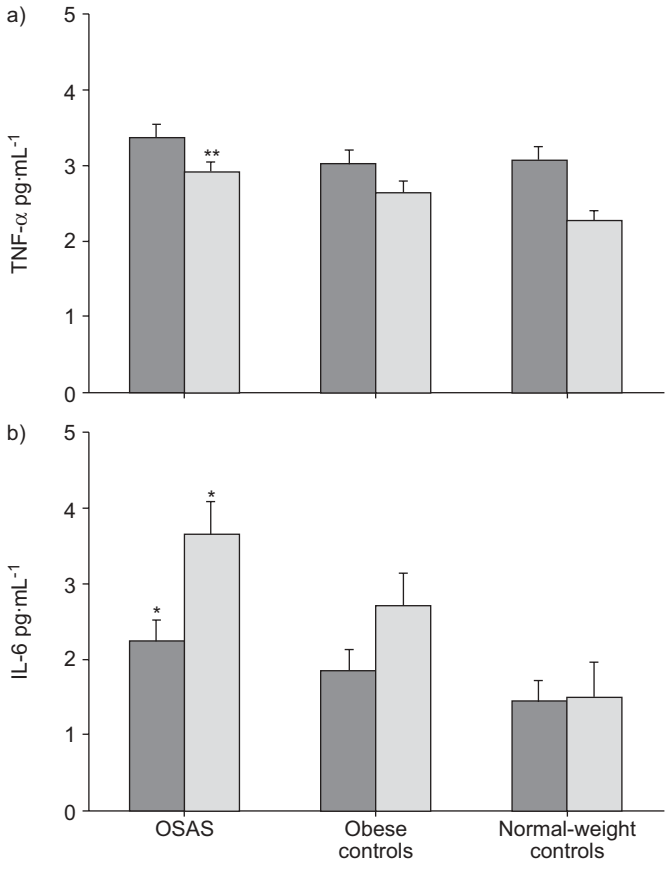

FIGURE 2. Inflammatory cytokines a) tumour necrosis factor (TNF)-α and b) interleukin (IL)-6 and sleepiness in obstructive apnoea/hypopnoea syndrome (OSAHS). ■: before 12 noon; ■: after 12 noon. *: $p<0.05$; **: $p<0.01$. Reproduced from [12] with permission from the publisher.

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,

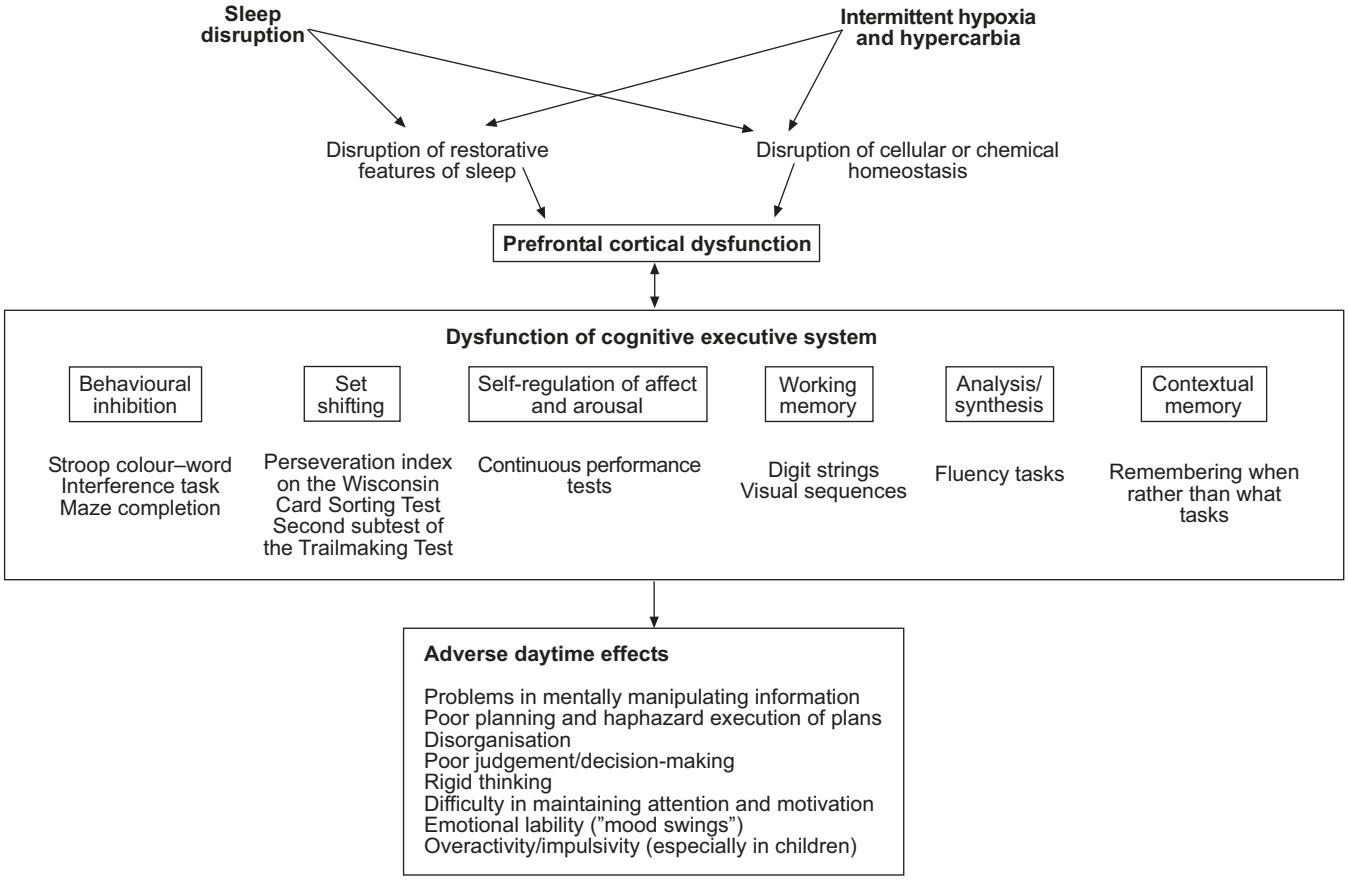

FIGURE 3. The generally accepted prefrontal obstructive sleep apnoea/hypopnea syndrome executive dysfunction model. Adapted from [16] with permission from the publisher.

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.

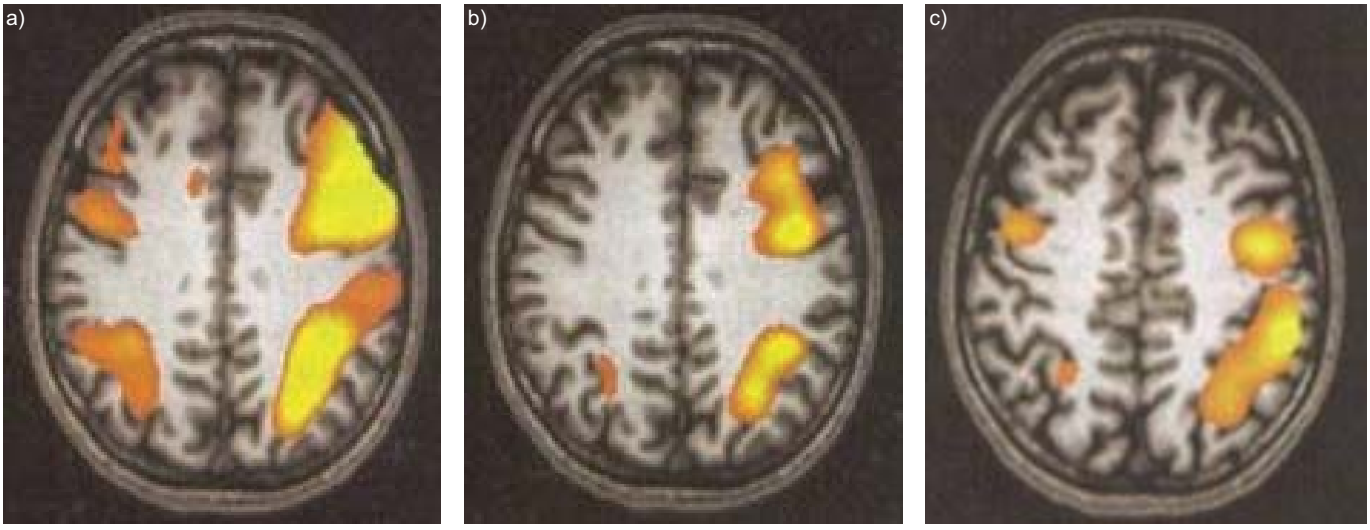

FIGURE 4. Functional magnetic resonance imaging of brain activation during a working memory task in healthy subjects *versus* patients with obstructive sleep apnoea/hypopnea syndrome (OSAHS) before and after continuous positive airway pressure treatment. Group activation map comparing a) 10 healthy subjects, 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, MOSKOWITCH [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, MAZZA *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 AHI >10 events·h^{-1} 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

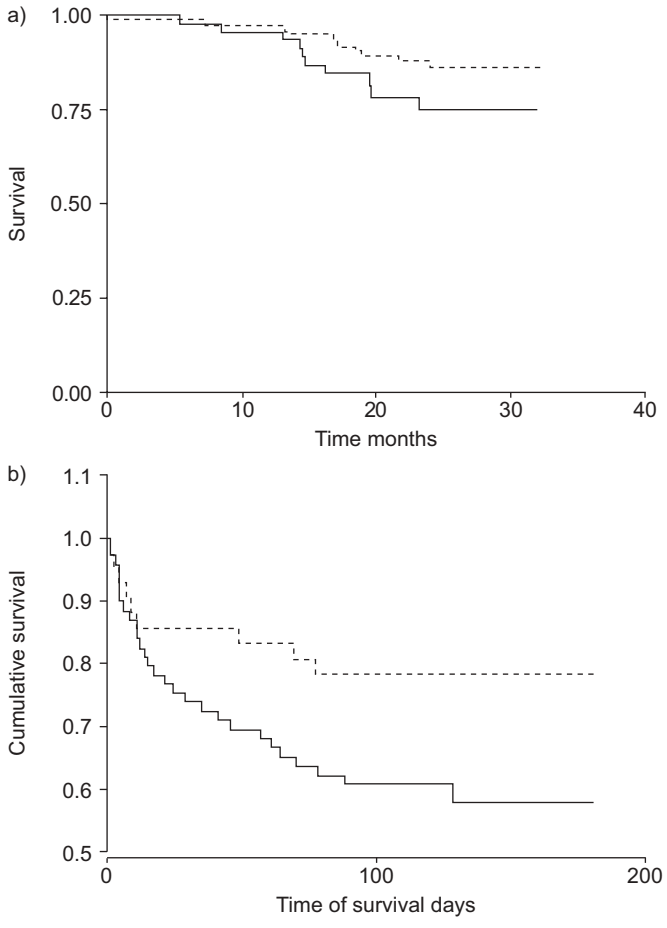

FIGURE 5. Differences in the survival of post-stroke patients demonstrating obstructive sleep apnoea/hypopnoea syndrome (OSAHS) *versus* no OSAHS in the immediate, acute post-stroke period with a) apnoea/hypopnoea index (AHI) $\geqslant$30 or $<$30 events·h^{-1}, and b) AHI $>$10 or $<$10 events·h^{-1}. a) ——: AHI $\geqslant$30 events·h^{-1}; ------: AHI $<$30 events·h^{-1}; b) ——: AHI $>$10 events·h^{-1}; -----: AHI $<$10 events·h^{-1}; $p<0.04$. Reproduced from [48, 49] with permission from the publishers.

6 months. Conversely, in the study by TURKINGTON *et al.* [49], logistic regression analysis taking into account different possible confounders demonstrated that both stroke severity and severity of upper airway collapse were independently associated with dependency in the long term. In addition, the investigators demonstrated that patients with AHI >10 events·h^{-1} who survived at 6 months spent a longer time in hospital than those with AHI <10 events·h^{-1}.

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].

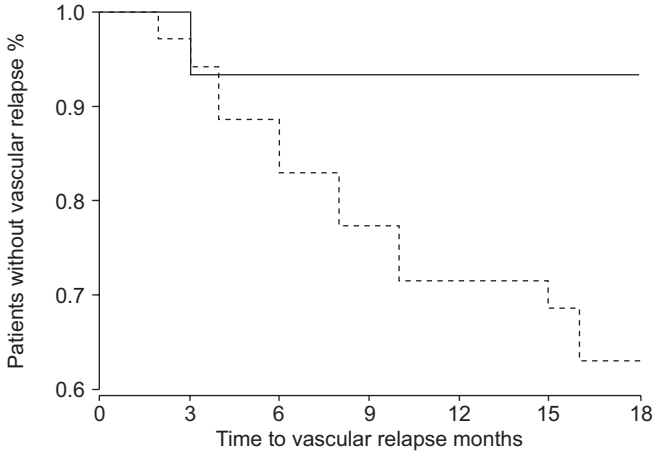

FIGURE 6. The impact of continuous positive airway pressure (CPAP) on relapse of cerebrovascular ischaemic events (VEs) in stroke patients presenting with an apnoea/hypopnoea index (AHI) of ⩾20 events·h^{-1} in the rehabilitation period. In this study, CPAP was prescribed in 51 patients with stroke demonstrating an AHI ⩾20 events·h^{-1} 2 months after the acute phase; the incidence of new VEs during a follow-up period of 18 months was greater in the group who did not tolerate CPAP (group II: ------; n=36) *versus* the CPAP users (group I: ——; n=15). New VEs occurred in 36.1 and 6.7% of patients, respectively, in group I and II. Reproduced from [53] with permission from the publisher.

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

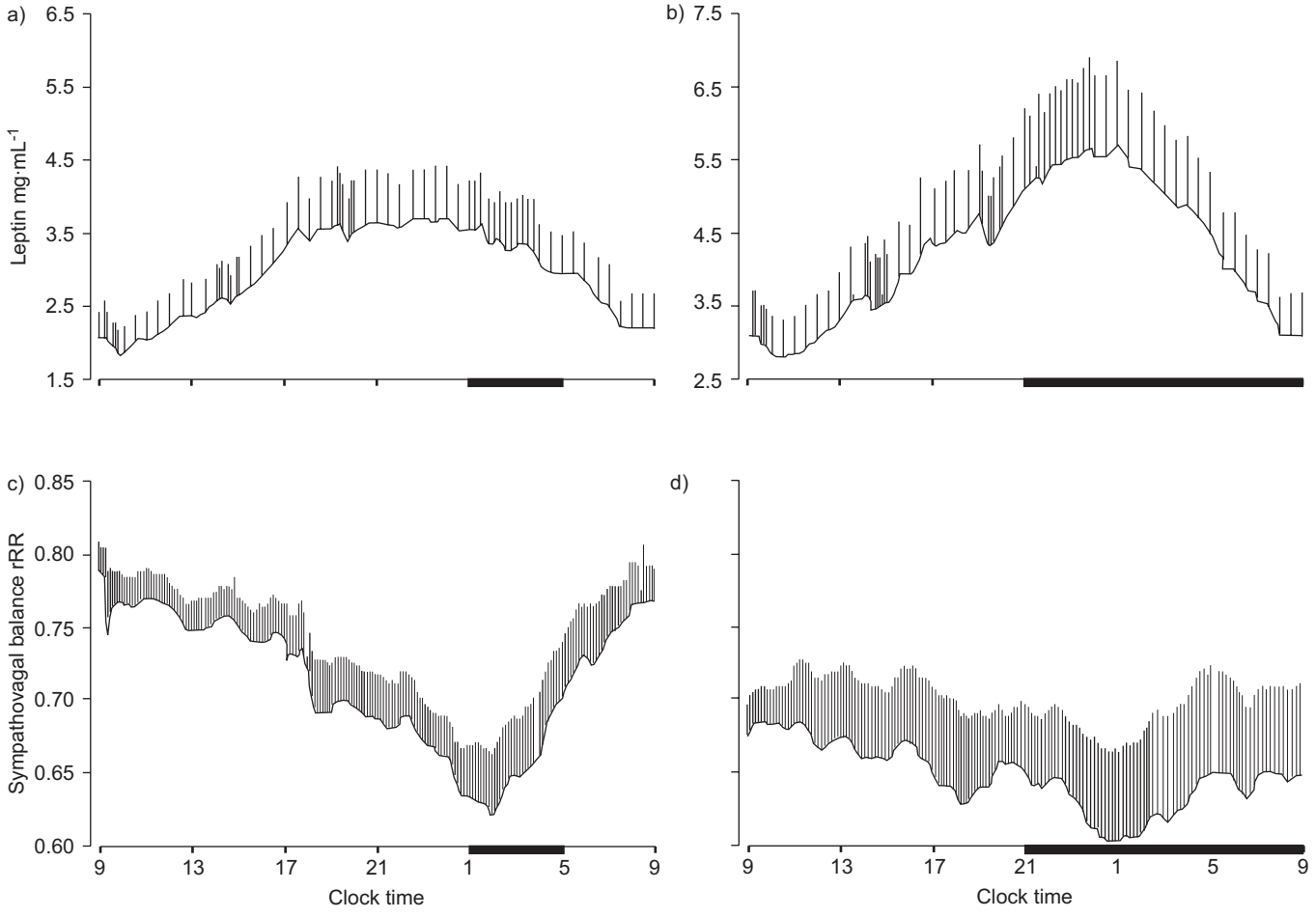

FIGURE 7. a) and b) Levels of leptin and c) and d) sympathovagal balance after six nights of a) and c) 4 h in bed with 3 h 49 min sleep and b) and d) 12 h in bed with 9 h 3 min of sleep. The dark box on the horizontal axes represents the time spent in bed. Decreased leptin levels after sleep curtailment appear to be due to increased sympathovagal balance. rRR: autocorrelation coefficient of consecutive interbeat interval analysis of heart rate variability. Reproduced from [63] with permission from the publisher.

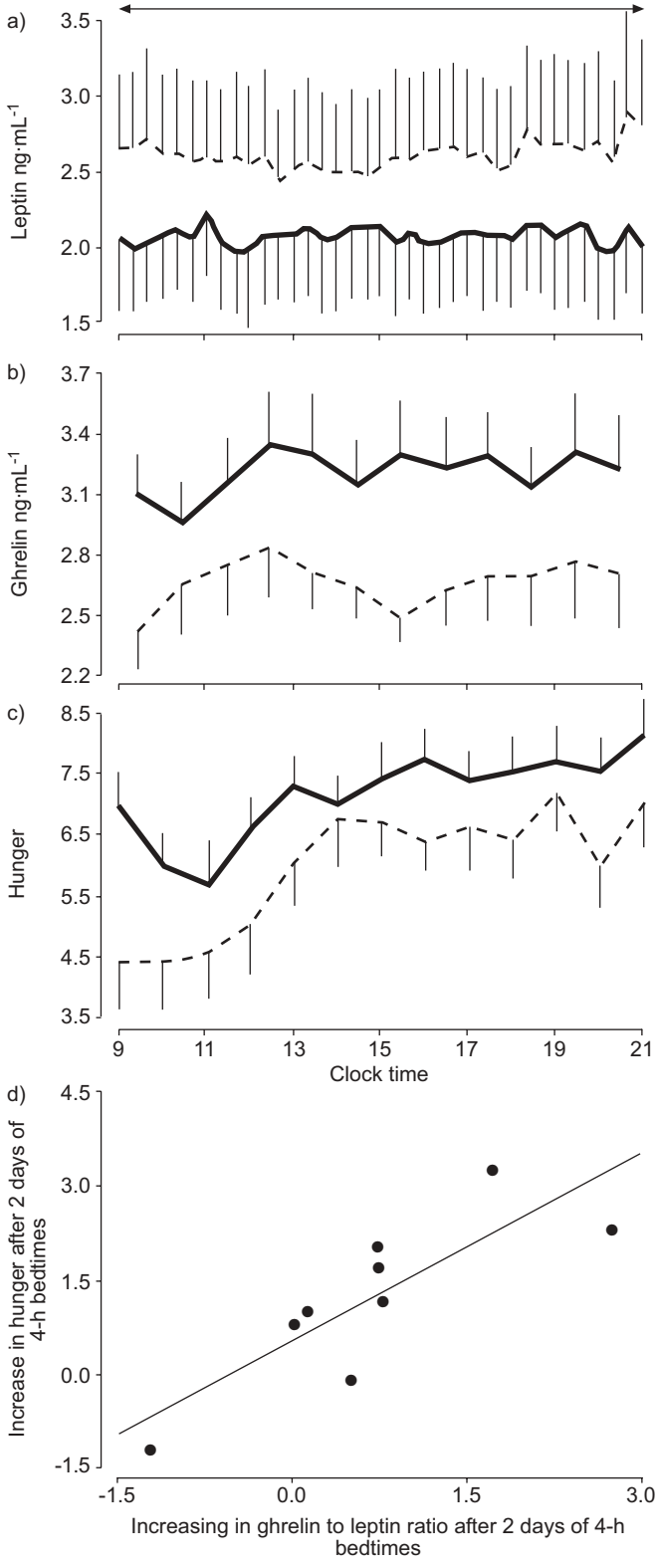

FIGURE 8. a)–c) Sleep restriction (———) compared with sleep extension (-----) under controlled conditions of caloric intake (arrow: continuous glucose infusion of 5 mg·kg^{-1} per 24 h) results in decrease in daytime leptin (a) and increase in daytime ghrelin levels (b) accompanied by increase in hunger (c) strongly correlated with the changes in leptin/ghrelin ratio (d). d) Spearman coefficient=0.867, p=0.014. Reproduced from [64] with permission from the publisher.

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

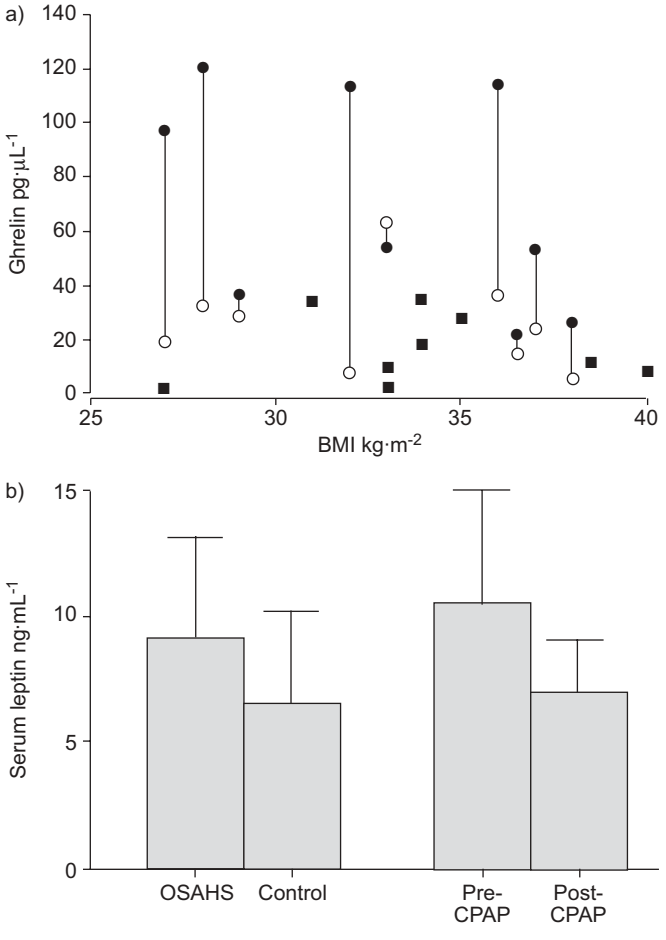

FIGURE 9. a) Ghrelin and b) leptin levels in obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and the impact of continuous positive airway pressure (CPAP) treatment. a) Ghrelin levels are higher in untreated OSAHS patients (●) than in body mass index (BMI)-matched controls (■), and decrease to levels only slightly higher than BMI-matched controls after only 2 days of CPAP (○), n=9. 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 hypervagotonia 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 hypocapnia with impact on the carbon dioxide tension–apnoeic 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 syncope 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

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	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
Δ nocturnal heart rate beats·min^{-1}	18$^{\#}$	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.

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 geniohyoid 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 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$^{\#}$
OAHI without pacing events·h^{-1}		10±12
ΔOAHI 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; OAHI: obstructive apnoea/hypopnoea index. $^{\#}$: statistically significant; ¶: all patients demonstrated central sleep apnoea on polygraphy.

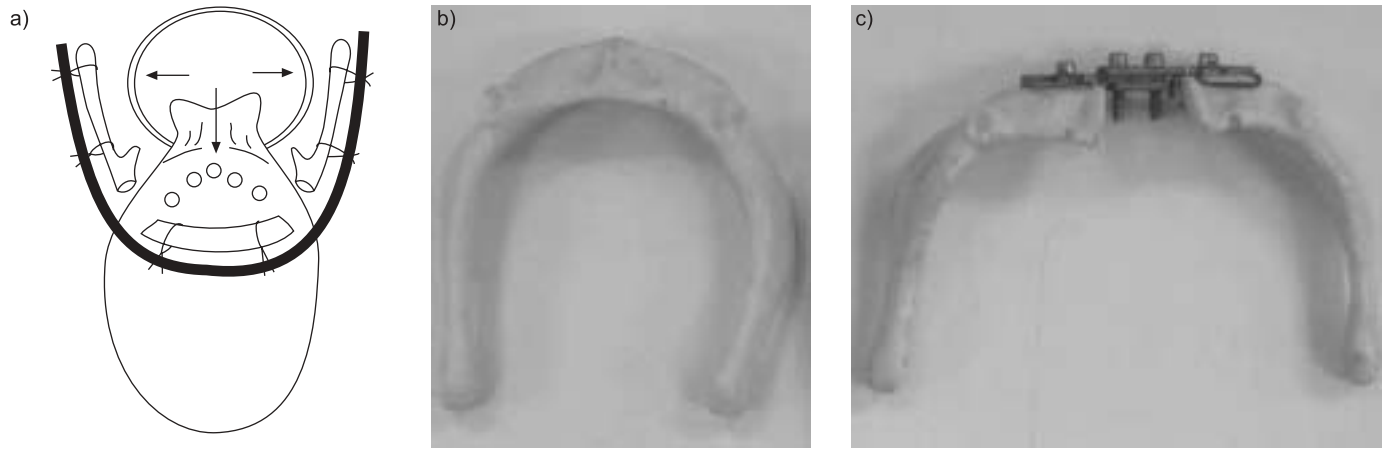

FIGURE 10. Expansion hyoidoplasty. a) Trisection of the hyoid bone held by an expansion brace, increasing the pharyngeal area in lateral and sagittal direction, a technique demonstrated to be effective in animal (dog) models. A safe procedure, as tested in humans in a pilot study involves b) the hyoid bone being split into two parts and (c) a titanium implant (Air Frame™ system; Aspire Medical, Palo Alto, CA, USA) being placed in-between. Reproduced from [98] with permission from the publisher.

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) $kg \cdot m^{-2}$ and AHI 28 (20–48) $events \cdot h^{-1}$. 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.

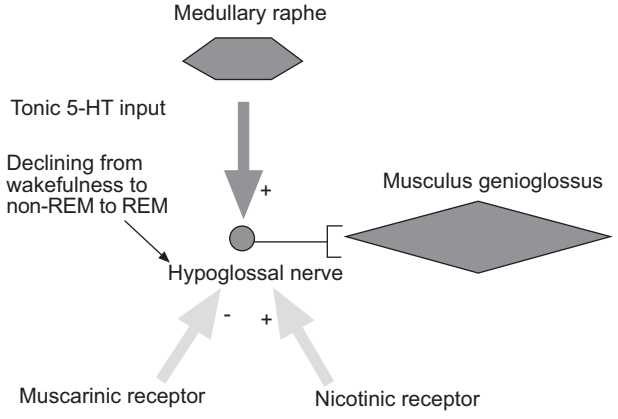

FIGURE 11. Serotonergic and cholinergic innervation of the hypoglossal nerve. 5-HT: 5-hydroxytryptamine (serotonin); REM: rapid eye movement.

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. Protryptiline 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 serotonergic 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 SSRI) 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-HT_1 receptor, and antagonist at 5-HT_2 and 5-HT_3 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-HT_2 and 5-HT_3 antagonistic effects appear to be a positive point: systemic injection of serotonin in rats has shown to produce apnoea, an effect mediated by 5-HT_2 and 5-HT_3 receptors in or on the nodose ganglia [119]; moreover, administration of mirtazapine (possessing both 5-HT_2 and 5-HT_3 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 untill 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 neurones 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 anti-cholinesterase 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. HEDNER *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) Progestin 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-electromyogram (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 increase of ventilatory drive during the 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

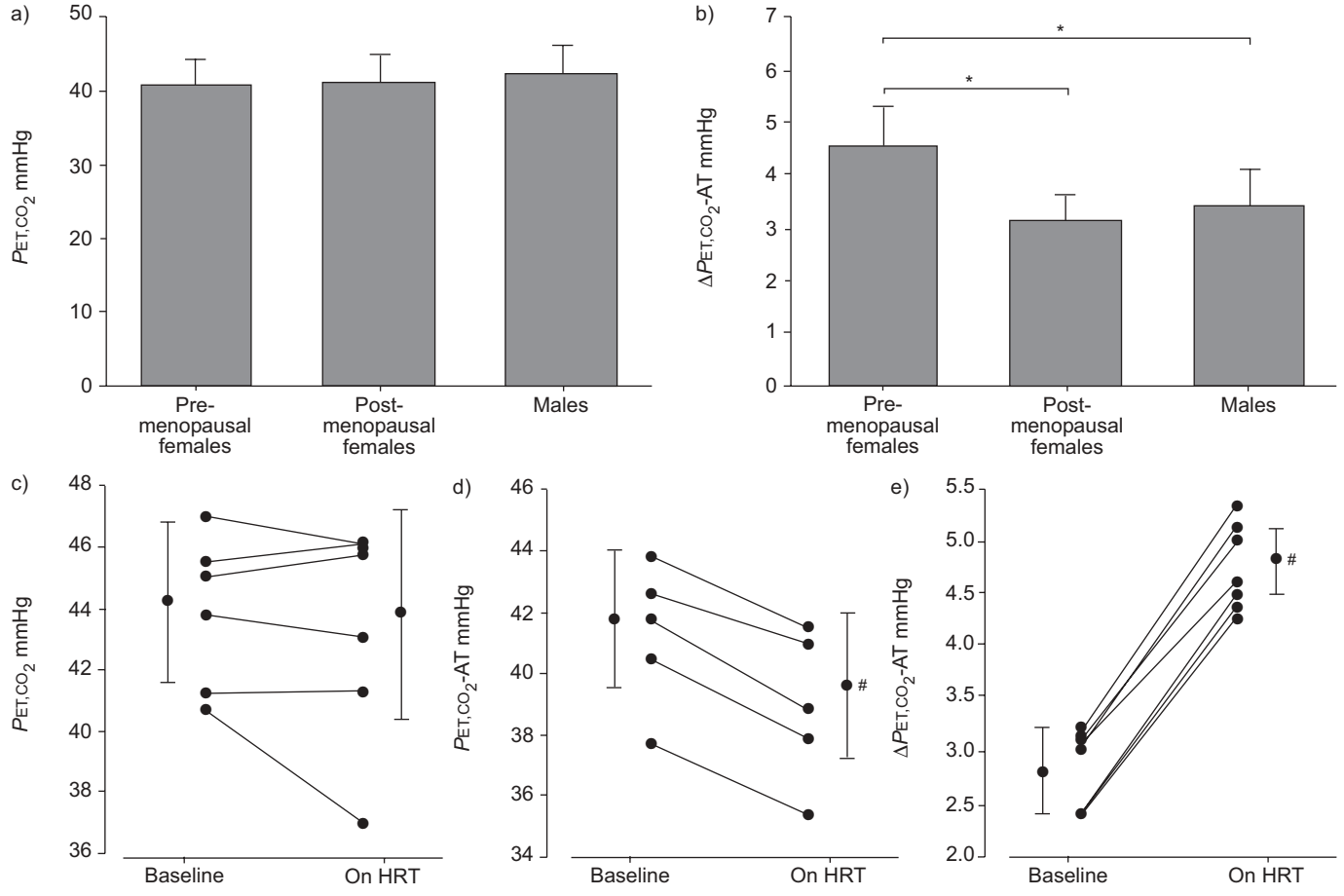

FIGURE 12. End-tidal carbon dioxide tension (P_{ET,CO_2}), P_{ET,CO_2} apnoeic thresholds (P_{ET,CO_2}-AT) and differences between baseline P_{ET,CO_2} and the P_{ET,CO_2}-AT ($\Delta P_{ET,CO_2}$-AT) in pre- and post-menopausal females compared with post-menopausal females and males. a) There was no significant difference in the P_{ET,CO_2}-AT between groups. b) $\Delta P_{ET,CO_2}$-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) P_{ET,CO_2}, d) P_{ET,CO_2}-AT, and e) $\Delta P_{ET,CO_2}$-AT at baseline and after 1 month of hormone replacement therapy (HRT) in post-menopausal females showed that P_{ET,CO_2}-AT was significantly decreased and $\Delta P_{ET,CO_2}$-AT significantly increased with HRT treatment. #: P_{ET,CO_2}-AT was significantly decreased and $\Delta P_{ET,CO_2}$-AT significantly increased with HRT. *: p=0.05. 1 mmHg = 0.133 kPa. Reproduced from [148] with permission from the publisher.

TABLE 3 Summary of interventional studies on hormone replacement therapy (HRT)

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+estrogen	Progestin+oestrogen		HVR increase, HCVR unchanged
Collop [152]	Randomised, double-blinded, placebo-controlled, crossover	8	Progestin	1 week	Yes Oxygen saturation increase
Keefe [153]	Open label	5	Oestrogen Followed by progestin+oestrogen	3–4 weeks 12 days	Yes 25% reduction in oestrogen group; 50% in combined therapy group
Manber [154]	Open label	6	Oestrogen + placebo during 6–13 days Followed by progestin+oestrogen during 6–13 days	6–13 days 6–13 days	Yes Oestrogen: reduced AHI (effect size 0.5) Attenuation of the effect by additional use progestin
Wesström [155]	Open label	5	Progestin+oestrogen	5–6 weeks	Yes (75% reduction in AHI)
Saaresranta [156]	Open label	10	Progestin	14 days	Static charge sensitive bed: AHI unchanged (low value at baseline) IRR pattern unchanged Decrease in mean P_{ET,CO_2} over the night
Polo-Kantola [157]	Randomised, double-blind, placebo-controlled, cross-over	62	Oestrogen	3 months	Static charge-sensitive bed: Yes IRR pattern unchanged
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.

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

provided by the population-based epidemiology study by BIXLER *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 BIXLER *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].

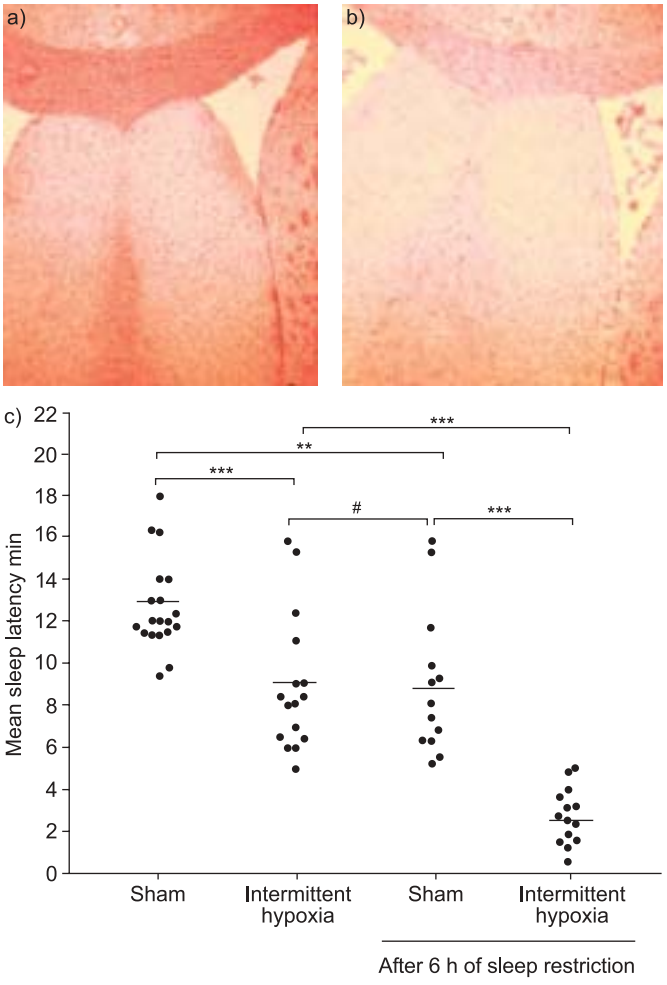

FIGURE 13. Impact of intermittent hypoxia on the brains and sleepiness of mice. a) and b) Staining with 2,4-dinitrophenyl hydrazone (a marker of protein oxidation indicating brain injury) in sleep-wake brain regions in the basal forebrain of mice. The staining is more pronounced in mice exposed to intermittent hypoxia (a) than in sham mice (b). c) The mean sleep latency is shorter in mice exposed to intermediate hypoxia, and the shortening is especially obvious after sleep curtailment. #: not significant. **: $p<0.01$; ***: $p<0.001$. Reproduced from [163] with permission from the publishers.

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].

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].

TABLE 4 Overview of the modafinil trials in obstructive sleep apnoea/hypopnoea patients on continuous positive airway pressure (CPAP) with refractory sleepiness

First author [ref.]	Study design	n	Dose mg	Benefit	Adverse events
Kingshott [174]	Randomised, double-blind, placebo-controlled, cross-over	30	400/2 weeks	ESS unchanged ↑ alertness on MWT MSLT unchanged Cognitive performance unchanged QoL unchanged	Nausea Dry mouth ↓ CPAP use (from 6.5–6.3 h·night^{-1})
Pack [175]	Randomised, double-blind, placebo-controlled, parallel	77 on modafinil 80 on placebo	200 (week 1) 400 (weeks 2–4)	↓ sleepiness on ESS ↓ sleepiness on MSLT	Headache CPAP use unchanged
Schwartz [176]	Open label	125	200–400 mg (individually titrated) during 12 weeks	↓ sleepiness on ESS ↑ QOL on FOSQ	Anxiety Headache Nausea Insomnia ↓ CPAP use (from 6.3–5.9 h·night^{-1})
Black [177]	Randomised, double-blind, placebo-controlled, parallel (three arms)	101 using 400 mg, 104 using 200 mg	400 mg 200 mg during 12 weeks	↓ sleepiness on ESS ↑ alertness on MWT ↑ QOL on FOSQ	Headache Nausea CPAP use unchanged

ESS: Epworth sleepiness scale; ↑: increase; MWT: multiple wakefulness test; MSLT: multiple sleep latency test; ↓: decrease; QoL: quality-of-life questionnaire; FOSQ: functional outcomes of sleep questionnaire.

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 [171, 172], and the benefit of modafinil on alertness is largely reduced in animals already co-treated with norepinephrine α- or β-blocker agents (a condition quite frequent in OSAHS patients with hypertension). The drug has an excellent benefit/risk ratio; it provides a long-lasting alerting effect with a low (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 AHI of the study sample while on CPAP treatment was 8 and the arousal index was 28. Although the mean pre-treatment AHI 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

Working group 2. France: I. Arnulf (Paris), S. Launois-Rollinat, P. Lévy (Grenoble); Germany: H. Becker (Marburg), T. Penzel, (Berlin), I. Harsch (Erlangen), L. Lüthje (Göttingen); Sweden: L. Grote, J. Hedner, (Gothenburg); Belgium: E. Hamans (Antwerp), R. Poirrier (Liège), K. Spiegel, (Brussels); USA: S. Javaheri (Mason, OH); Israel: L. Lavie, P. Lavie (Haïfa); Finland: T. Saaresranta (Turku); UK: I. Smith (Cambridge), E. Verstraeten (Swansea), P. Turkington (Salford).

The present article was presented as part of the international symposium ''Respiratory somnology: a clinical update'', sponsored by GlaxoSmithKline, Belgium. T. Penzel has received reimbursement for conference attendance and speaker fees from Respironics and Weinmann. L. Grote has received research funding from Breas Medical AB, ResMed, Respironics, Weinmann, Itamar Medical Ltd and Pfizer. L. Grote has also received speaker and educational fees from ResMed, Respironics, Weinmann and Pfizer. S. Javaheri has acted as a consultant for, and received honoraria for lectures and research from, Respironics and ResMed. P. Lavie is a founder and board member of Itamar Medical Ltd, SLP Ltd, Sleep Health Centers US and Sleep Disorders Center Israel; he owns options and shares in these companies. I. Smith has received travel grants and honoraria from Cephalon, UK. His research staff have been funded by unrestricted educational grants from ResMed and Friday Medical Ltd. I. Arnulf has received speaker fees from Cephalon Ltd.

REFERENCES

1 Chugh DK, Dinges DF. Mechanisms of sleepiness in obstructive sleep apnea. *In*: Pack AI, ed. Sleep Apnea. Pathogenesis, Diagnosis and Treatment. New York, Marcel Dekker, 2002; pp. 265–285.
2 Roehrs T, Zorick F, Wittig R, Conway W, Roth T. Predictors of objective level of daytime sleepiness in patients with sleep-related breathing disorders. *Chest* 1989; 95: 1202–1206.
3 Colt HG, Haas H, Rich GB. Hypoxemia *vs* sleep fragmentation as cause of excessive daytime sleepiness in obstructive sleep apnea. *Chest* 1991; 100: 1542–1548.
4 Kingshott RN, Engleman HM, Deary IJ, Douglas NJ. Does arousal frequency predict daytime function? *Eur Respir J* 1998; 12: 1264–1270.
5 Chervin RD, Aldrich MS. Characteristics of apneas and hypopneas during sleep and relation to excessive daytime sleepiness. *Sleep* 1998; 21: 799–806.
6 Bennett LS, Langford BA, Stradling JR, Davies RJ. Sleep fragmentation indices as predictors of daytime sleepiness and nCPAP response in obstructive sleep apnea. *Am J Respir Crit Care Med* 1998; 158: 778–786.
7 Kingshott RN, Vennelle M, Hoy CJ, Engleman HM, Deary IJ, Douglas NJ. Predictors of improvements in daytime function outcomes with CPAP therapy. *Am J Respir Crit Care Med* 2000; 161: 866–871.
8 Gottlieb DJ, Whitney CW, Bonekat WH, *et al.* Relation of sleepiness to respiratory disturbance index. The Sleep Heart Health Study. *Am J Respir Crit Care Med* 1999; 159: 502–507.
9 Bixler EO, Vgontzas AN, Lin HM, Calhoun SL, Vela-Bueno A, Kales A. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol Metab* 2005; 90: 4510–4515.
10 Buyse B, Hedner J, the participants of working group 2. Sleep apnoea, hypertension and vascular disease: where are we now? *Eur Respir Rev* 2007; 16: 169–182.
11 Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP. Elevation of plasma cytokines in disorders of excessive sleepiness: role of sleep disturbance and obesity. *J Clin Endocrinol Metab* 1997; 82: 1313–1316.
12 Vgontzas AN, Papanicolaou DA, Bixler EO, *et al.* Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* 2000; 85: 1151–1158.
13 Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakade G, Chrousos GP. Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-α antagonist. *J Clin Endocrinol Metab* 2004; 89: 4409–4413.
14 Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: results of a meta-analysis. *Arch Intern Med* 2003; 163: 565–571.
15 Fulda S, Shulz H. Cognitive dysfunction in sleep disorders. *Sleep Med Rev* 2001; 5: 423–445.
16 Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. *J Sleep Res* 2002; 11: 1–16.
17 Verstraeten E, Cluydts R. Executive control of attention in sleep apnea patients: theoretical concepts and methodological considerations. *Sleep Med Rev* 2004; 8: 257–267.

18 Verstraeten E, Cluydts R, Pevernagie D, Hoffmann G. Executive function in sleep apnea: controlling for attentional capacity in assessing executive attention. *Sleep* 2004; 27: 685–693.
19 Thomas RJ, Rosen BR, Stern CHE, Weiss JW, Kwong KK. Functional imaging of working memory in obstructive sleep-disordered breathing. *J Appl Physiol* 2005; 98: 2226–2234.
20 Gozal D, Kheirandish L. Sleepiness and neurodegenaration in sleep-disordered breathing: convergence of signaling cascades. *Am J Respir Crit Care Med* 2005; 171: 1325–1327.
21 Krieger J. Sleep apnoea and driving: how can this be dealt with? *Eur Respir Rev* 2007; 16: 189–195.
22 Leger D. The cost of sleep-related accidents: a report for the National Commission on Sleep Disorders Research. *Sleep* 1994; 17: 84–93.
23 Webb WB. The cost of sleep-related accidents: a reanalysis. *Sleep* 1995; 18: 276–80.
24 Gurubhagavatula I, Maislin G, Nkwuo JE, Pack AI. Occupational screening for obstructive sleep apnea in commercial drivers. *Am J Respir Crit Care Med* 2004; 170: 371–376.
25 Moskowitch A. Pilot development and testing of cost effective approach to screening, diagnosis, treatment of sleep apnea in commercial motor carriers. *Sleep Medicine* 2005; 6: Suppl. 2, S58 (abstract 026).
26 Turkington PM, Sircar M, Allgar V, Elliott MW. Relationship between obstructive sleep apnoea, driving simulator performance, and risk of road traffic accidents. *Thorax* 2001; 56; 800–805.
27 Philip P, Sagaspe P, Taillard J, *et al*. Fatigue, sleepiness, and performance in simulated *versus* real driving conditions. *Sleep* 2005; 28; 1511–1516.
28 Wise MS. Objective measures of sleepiness and wakefulness: application to the real world? *J Clin Neurophysiol* 2006; 23; 39–49.
29 Bennett LS, Stradling JR, Davies RJ. A behavioural test to assess daytime sleepiness in obstructive sleep apnoea. *J Sleep Res* 1997; 6; 142–145.
30 Krieger AC, Ayappa I, Norman RG, Rapoport DM, Walsleben J. Comparison of the maintenance of wakefulness test (MWT) to a modified behavioral test (OSLER) in the evaluation of daytime sleepiness. *J Sleep Res* 2004; 13; 407–411.
31 George CF. Driving simulators in clinical practice. *Sleep Med Rev* 2003; 7; 311–320.
32 Findley LJ, Fabrizio MJ, Knight H, Norcross BB, LaForte AJ, Suratt PM. Driving simulator performance in patients with sleep apnea. *Am Rev Respir Dis* 1989; 140; 529–530.
33 Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. *Lancet* 1994; 343; 572–575.
34 Hack M, Davies RJ, Mullins R, *et al*. Randomised prospective parallel trial of therapeutic *versus* subtherapeutic nasal continuous positive airway pressure on simulated steering performance in patients with obstructive sleep apnoea. *Thorax* 2000; 55; 224–231.
35 Turkington PM, Sircar M, Saralaya D, Elliott MW. Time course of changes in driving simulator performance with and without treatment in patients with sleep apnoea hypopnoea syndrome. *Thorax* 2004; 59; 56–59.
36 Orth M, Duchna HW, Leidag M, *et al*. Driving simulator and neuropsychological testing in OSAS before and under CPAP therapy. *Eur Respir J* 2005; 26; 898–903.
37 Mazza S, Pépin JL, Naëgelé B, Plante J, Deschaux C, Lévy P. Most obstructive sleep apnoea patients exhibit vigilance and attention deficits on an extended battery of tests. *Eur Respir J* 2005; 25: 75–80.
38 Edinger JD, Radke RA. Use of *in vivo* desensitization to treat a patient's claustrophobic response to nasal CPAP. *Sleep* 1993; 16: 678–680.
39 Weaver TE, Maislin G, Dinges DF, *et al*. Self-efficacy in sleep apnea: instrument development and patient perceptions of obstructive sleep apnea risk, treatment benefit, and volition to use continuous positive airway pressure. *Sleep* 2003; 26: 727–732.
40 Stepnowsky CJ Jr, Bardwell WA, Moore PJ, Ancoli-Israel S, Dimsdale JE. Psychologic correlates of compliance with continuous positive airway pressure. *Sleep* 2002; 25: 758–762.
41 Javaheri S. Treatment of obstructive and central sleep apnoea in heart failure: practical options. *Eur Respir Rev* 2007; 16: 183–188.
42 Yaggi H, Mohsenin V. Obstructive sleep apnoea and stroke. *Lancet Neurol* 2004; 3: 333–342.
43 Hui D, Choy D, Wong L, *et al*. Prevalence of sleep-disordered breathing and continuous positive airway pressure compliance. *Chest* 2002; 122: 852–860.
44 Bassetti C, Aldrich MS. Sleep apnoea in acute cerebrovasular diseases: final report on 128 patients. *Sleep* 1999; 22: 217–223.
45 Wessendorf TE, Teschler H, Wang YM, Konietzko N, Thilmann AF. Sleep-disordered breathing among patients with first-ever stroke. *J Neurol* 2000; 247: 41–47.
46 Lawrence E, Dundas R, Higgens S, *et al*. The natural history and associations of sleep disordered breathing in first ever stroke. *Int J Clin Pract* 2001; 55: 584–588.
47 Harbison J, Ford GA, James OFW, Gibson GJ. Sleep-disordered breathing following acute stroke. *Q J Med* 2002; 95: 741–742.
48 Parra O, Arboix A, Montserrat JM, Quinto L, Bechich S, Garcia-Eroles L. Sleep-related breathing disorders: impact on mortality of cerebrovascular disease. *Eur Respir J* 2004; 24: 267–272.
49 Turkington PM, Allgar V, Bamford J, Wanklyn P, Elliott MW. Effect of upper airway obstruction in acute stroke on functional outcome at 6 months. *Thorax* 2004; 59: 367–371.
50 Iranzo A, Santamaria J, Berenguer J, Sanchez M, Chamorro A. Prevalence and clinical importance of sleep apnea in the first night after cerebral infarction. *Neurology* 2002; 58: 911–916.
51 Sandberg O, Franklin KA, Bucht G, Eriksson S, Gustafson Y. Nasal continuous positive airway pressure in stroke patients with sleep apnoea: a randomized treatment study. *Eur Respir J* 2001; 18: 630–634.
52 Wessendorf TE, Wang YM, Thilmann AF, Sorgenfrei U, Konietzko N, Teschler H. Treatment of obstructive sleep apnoea with nasal continuous positive airway pressure in stroke. *Eur Respir J* 2001; 18: 623–629.

53 Martinez-Garcia MA, Galiano-Blancart R, Roman-Sanchez P, Soler-Cataluna JJ, Cabero-Salt L, Salcedo-Maiques E. Continuous positive airway pressure treatment in sleep apnea prevents new vascular events after ischemic stroke. *Chest* 2005; 128: 2123–2129.

54 Scala R, Turkington PM, Wanklyn P, Bamford J, Elliott MW. Effects of incremental levels of continuous positive airway pressure on cerebral blood flow velocity in healthy adult humans. *Clin Sci (Lond)* 2003; 104: 633–639.

55 Turkington PM, Bamford J, Wanklyn P, Elliott MW. Prevalence and predictors of upper airway obstruction in the first 24 hours after acute stroke. *Stroke* 2002; 33: 2037–2042.

56 Harsch IA. Metabolic disturbances in patients with obstructive sleep apnoea syndrome. *Eur Respir Rev* 2007; 16: 196–202.

57 Broberger C. Brain regulation of food intake and appetite: molecules and networks. *J Intern Med* 2005; 258: 301–327.

58 Sharma V, McNeill JH. The emerging roles of leptin and ghrelin in cardiovascular physiology and pathophysiology. *Curr Vasc Pharmacol* 2005; 3: 169–180.

59 Kripke DF, Simons RN, Garfinkel L, Hammond EC. Short and long sleep and sleeping pills. Is increased mortality associated? *Arch Gen Psychiatry* 1979; 36: 103–116.

60 National Sleep Foundation, ''Sleep in America'' Poll. Washington, DC, National Sleep Foundation, 2000, 2001, 2002.

61 Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960–1994. *Int J Obes Relat Metab Disord* 1998; 22: 39–47.

62 Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA* 2002; 288: 1723–1727.

63 Spiegel K, Leproult R, L'hermite-Baleriaux M, Copinschi G, Penev PD, Van Cauter E. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. *J Clin Endocrinol Metab* 2004; 89: 5762–5771.

64 Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004; 141: 846–850.

65 Rayner DV, Trayhurn P. Regulation of leptin production: sympathetic nervous system interactions. *J Mol Med* 2001; 79: 8–20.

66 Sugino T, Yamaura J, Yamagishi M, *et al.* Involvement of cholinergic neurons in the regulation of the ghrelin secretory response to feeding in sheep. *Biochem Biophys Res Commun* 2003; 304: 308–312.

67 Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med* 2004; 1: e62.

68 Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *Sleep* 2004; 27: Suppl. A, 146–147.

69 Bassiri AG, Guilleminault C. Clinical features and evaluation of obstructive sleep apnea–hypopnea syndrome. *In*: Kryger MH, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine. 3rd Edn. Philadelphia, PA, W.B. Saunders, 2000; pp. 869–878.

70 Persson HE, Svanborg E. Sleep deprivation worsens obstructive sleep apnea. Comparison between diurnal and nocturnal polysomnography. *Chest* 1996; 109: 645–650.

71 Phillips BG, Hisel TM, Kato M, *et al.* Recent weight gain in patients with newly diagnosed obstructive sleep apnea. *J Hypertens* 1999; 17: 1297–300.

72 Phillips BG, Kato M, Narkiewicz K, Choe I, Somers VK. Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. *Am J Physiol Heart Circ Physiol* 2000; 279: H234–H237.

73 Harsch IA, Konturek PC, Koebnick C, *et al.* Leptin and ghrelin levels in patients with obstructive sleep apnoea: effect of CPAP treatment. *Eur Respir J* 2003; 22: 251–257.

74 Ip S, Lam K, Ho C, Tsang K, Lam W. Serum leptin and vascular risk factors in obstructive sleep apnea. *Chest* 2000; 118: 580–586.

75 Saarelainen S, Lahtela J, Kallonen E. Effect of nasal CPAP treatment on insulin sensitivity and plasma leptin. *J Sleep Res* 1997; 6: 146–147.

76 Chin K, Shimizu K, Nakamura T, *et al.* Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation* 1999; 100: 706–712.

77 Shimizu K, Chin K, Nakamura T, *et al.* Plasma leptin levels and cardiac sympathetic function in patients with obstructive sleep apnoea–hypopnoea syndrome. *Thorax* 2002; 57: 429–434.

78 Sanner BM, Kollhosser P, Buechner N, Zidek W, Tepel M. Influence of treatment on leptin levels in patients with obstructive sleep apnoea. *Eur Respir J* 2004; 23: 601–604.

79 O'Donnell CP, Tankersley CG, Polotsky VP, Schwartz AR, Smith PL. Leptin, obesity, and respiratory function. *Respir Physiol* 2000; 119: 163–170.

80 Polotsky VY, Li J, Punjabi NM, *et al.* Intermittent hypoxia increases insulin resistance in genetically obese mice. *J Physiol* 2003; 552: 253–264.

81 Lavie P. Mortality in sleep apnoea syndrome: a review of the evidence. *Eur Respir Rev* 2007; 16: 203–210.

82 Garrigue S, Bordier P, Jais P, *et al.* Benefit of atrial pacing in sleep apnea syndrome. *N Engl J Med* 2002; 346: 404–412.

83 Gottlieb DJ. Cardiac pacing – a novel therapy for sleep apnea? *N Engl J Med* 2002; 346: 444–445.

84 Garrigue S, Bordier P, Barold SS, Clementy J. Sleep apnea: a new indication for cardiac pacing? *Pacing Clin Electrophysiol* 2004; 27: 204–211.

85 Shepard JW Jr, Pevernagie DA, Stanson AW, Daniels BK, Sheedy PF. Effects of changes in central venous pressure on upper airway size in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1996; 153: 250–254.

86 Alex CG, Onal E, Lopata M. Upper airway occlusion during sleep in patients with Cheyne–Stokes respiration. *Am Rev Respir Dis* 1986; 133: 42–45.

87 Badr MS, Kawak A, Skatrud JB, Morrell MJ, Zahn BR, Babcock MA. Effect of induced hypocapnic hypopnea on upper airway patency in humans during NREM sleep. *Respir Physiol* 1997; 110: 33–45.

88 Crick SJ, Sheppard MN, Anderson RH. Neural supply of the heart. *In*: Ter Horst GJ, ed. The Nervous System and the Heart. Totowa, NJ, Humana Press, 2000; pp. 3–54.

89 Orem J, Kubin L. Respiratory physiology: central neural control. *In*: Kryger MH, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine. 3rd Edn. Philadelphia, PA, W.B. Saunders, 2000; pp. 205–241.

90 Pepin JL, Defaye P, Garrigue S, Poezevara Y, Levy P. Overdrive atrial pacing does not improve obstructive sleep apnoea syndrome. *Eur Respir J* 2005; 25: 343–347.

91 Lüthje L, Unterberg-Buchwald C, Dajani D, Vollmann D, Hasenfuss G, Andreas S. Atrial overdrive pacing in patients with sleep apnea with implanted pacemaker. *Am J Respir Crit Care Med* 2005; 172: 118–122.

92 Simantirakis EN, Schiza SE, Chrysostomakis SI, *et al.* Atrial overdrive pacing for the obstructive sleep apnea–hypopnea syndrome. *N Engl J Med* 2005; 353: 2568–2577.

93 Unterberg C, Luthje L, Szych J, Vollmann D, Hasenfuss G, Andreas S. Atrial overdrive pacing compared to CPAP in patients with obstructive sleep apnoea syndrome. *Eur Heart J* 2005; 26: 2568–2575.

94 Krahn AD, Yee R, Erickson MK, *et al.* Physiologic pacing in patients with obstructive sleep apnea: a prospective, randomized crossover trial. *J Am Coll Cardiol* 2006; 47: 379–383.

95 Sinha AM, Skobel EC, Breithardt OA, *et al.* Cardiac resynchronization therapy improves central sleep apnea and Cheyne–Stokes respiration in patients with chronic heart failure. *J Am Coll Cardiol* 2004; 44: 68–71.

96 Gabor JY, Newman DA, Barnard-Roberts V, *et al.* Improvement in Cheyne–Stokes respiration following cardiac resynchronisation therapy. *Eur Respir J* 2005; 26: 95–100.

97 Floras JS, Bradley TD. Atrial overdrive pacing for sleep apnea. A door now closed? *Am J Respir Crit Care Med* 2005; 172: 1–5.

98 Patton TJ, Thawley SE, Waters RC, Vandermeer PJ, Ogura JH. Expansion hyoidplasty: a potential surgical procedure designed for selected patients with obstructive sleep apnea syndrome. Experimental canine results. *Laryngoscope* 1983; 93: 1387–1396.

99 Pevernagie DA, Stanson AW, Sheedy PF 2nd, Daniels BK, Shepard JW Jr, Effects of body position on the upper airway of patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1995; 152: 179–185.

100 den Herder C, van Tinteren H, de Vries N. Sleep endoscopy *versus* modified Mallampati score in sleep apnea and snoring. *Laryngoscope* 2005; 115: 735–739.

101 Smith IE, Quinnell TG. Pharmacotherapies for obstructive sleep apnoea: where are we now? *Drugs* 2004; 64: 1385–1399.

102 Kubin L, Tojima H, Davies RO, Pack AI. Serotonergic excitatory drive to hypoglossal motorneurons in the decerabrate cat. *Neurosci Lett* 1992; 139: 243–248.

103 Jacobs BL, Azmitia EC. Structure and function of the brain serotonin system. *Physiol Rev* 1992; 72; 165–229.

104 Richter DW, Manzke T, Wilken B, Ponimaskin E. Serotonin receptors: guardians of stable breathing. *Trends Mol Med* 2003; 9: 542–548.

105 Veasey SC. Serotonin agonists and antagonists in obstructive sleep apnea: therapeutic potential. *Am J Respir Med* 2003; 2: 21–29.

106 Veasey S. Pharmacotherapies for obstructive sleep apnea: how close are we? *Curr Opin Pulm Med* 2001; 7: 399–403.

107 Bonora M, St John WM, Bledsoe TA. Differential elevation by protriptyline and depression by diazepam of upper airway respiratory motor activity. *Am Rev Respir Dis* 1985; 131: 41–45.

108 Brownell LGP, West P, Sweatman P, Acres JC, Kryger MH. Protriptyline in obstructive sleep apnea: a double blind trial. *N Engl J Med* 1982; 307: 1037–1042.

109 Stepanski E, Conway W, Young D, Zorick FJ, Wittig RM, Roth T. A double blind trial of protriptyline in the treatment of sleep apnea syndrome. *Henry Ford Hosp Med J* 1988; 36: 5–8.

110 Whyte K, Gould G, Airlie A, Shapiro CM, Douglas NJ. Role of protriptyline and acetazolamide in the sleep apnoea/hypopnoea syndrome. *Sleep* 1988; 11: 463–472.

111 Sunderram J, Parisi RA, Strobel RJ. Serotonergic stimulation of the genioglossus and the response to nasal continuous positive airway pressure. *Am J Respir Crit Care Med* 2000; 162: 925–929.

112 Kraiczi H, Hedner J, Dahlof P, Ejnell H, Carlson J. Effect of serotonin uptake inhibition on breathing during sleep and daytime symptoms in obstructive sleep apnea. *Sleep* 1999; 22: 61–67.

113 Hanzel DA, Proia NG, Hudgel DW. Response of obstructive sleep apnea to fluoxetine and protriptyline. *Chest* 1991; 100: 416–421.

114 Veasey SC, Chachkes J Fenik P, Hendricks JC. The effects of ondansetron on sleep- disordered breathing in the English Bulldog. *Sleep* 2001; 24: 155–160.

115 Stradling J, Smith D, Radulovacki M, Carley C. Effect of ondansetron on moderate obstructive sleep apnoea, a single night, placebo-controlled trial. *J Sleep Res* 2003; 12: 169–170.

116 De Vane C. Differential pharmacology of newer antidepressants. *J Clin Psychiatry* 1998; 59: 85–93.

117 de Boer T. The pharmacologic profile of mirtazapine. *J Clin Psychiatry* 1996; 57: 19–25.

118 McNicholas W. Implications of pathophysiology for management of the obstructive sleep apnoea syndrome. *Monaldi Arch Chest Dis* 1998; 53: 524–529.

119 Yoshioka M, Goda Y, Togashi H, Matsumoto M, Saito H. Pharmacological characterization of 5-hydroxytryptamine-induced apnea in the rat. *J Pharmacol Exp Ther* 1992; 260: 917–924.

120 Carley DW, Radulovacki M. Mirtazapine, a mixed-profile serotonin agonist/antagonist, suppresses sleep apnea in the rat. *Am J Respir Crit Car Med* 1999; 160: 1824–1829.

121 Carley DW, Olopade C, Ruigt GS, Radulovacki M. Efficacy of mirtazapine in obstructive sleep apnoea syndrome. *Sleep* 2007; 30: 35–41.

122 Castillo JL, Menendez P, Segovia L, Guilleminault C. Effectiveness of mirtazapine in the treatment of sleep apnea/hypopnea syndrome (SAHS). *Sleep Med* 2004; 5: 507–508.

123 Liu X, Sood S, Liu H, Horner RL. Opposing muscarinic and nicotinic modulation of hypoglossal motor output to genioglossus muscle in rats *in vivo*. *J Physiol* 2005; 565: 965–980.

124 Shao XM, Feldman JL. Pharmacology of nicotinic receptors in preBötzinger complex that mediate modulation of respiratory pattern. *J Neurophysiol* 2002; 88: 1851–1858.

125 Gothe B, Strohl KP, Levin S, Cherniack NS. Nicotine: a different approach to treatment of obstructive sleep apnea. *Chest* 1985; 87: 11–17.

126 Davila DG, Hurt RD, Offord KP, Harris CD, Shepard JW Jr. Acute effects of transdermal nicotine on sleep architecture, snoring, and sleep-disordered breathing in nonsmokers. *Am J Respir Crit Care Med.* 1994; 150: 469–474.

127 Nilsson L, Nordberg A, Hardy J, Wester P, Winblad B. Physostigmine restores (^{3}H)acetylcholine efflux from Alzheimer brain slices to normal level. *J Neural Transm* 1986; 67: 275–285.

128 Hedner J, Craiczi H, Peker Y, Murphy P. Reduction of sleep-disordered breathing after physostigmine. *Am J Respir Crit Care Med* 2003; 168: 1246–1251.

129 Bellingham MC, Ireland MF. Contribution of cholinergic systems to state-dependent modulation of respiratory control. *Respir Physiol Neurobiol* 2002; 131: 135–144.

130 Burton MD, Kazemi H. Neurotransmitters in central respiratory control. *Respir Physiol* 2000; 122: 111–121.

131 Fitzgerald RS, Shirahata M, Wang HY. Acetylcholine is released from *in vitro* cat carotid bodies during hypoxic stimulation. *Adv Exp Med Biol* 2000; 475: 485–494.

132 Hedner E, Birkhed D, Hedner J, Ekström J, Helander H. Stimulation of minor salivary glands by intraoral treatment with the cholinesterase inhibitor physostigmine in man. *Eur J Oral Sci* 2001; 109: 371–374.

133 Jokic R, Klimaszewski A, Mink J, Fitzpatrick MF. Surface tension forces in sleep apnea: the role of a soft tissue lubricant: a randomized double-blind, placebo-controlled trial. *Am J Respir Crit Care Med* 1998; 157: 1522–1525.

134 Younes M. The physiologic basis of central apnea and periodic breathing. *Curr Pulmonol* 1989; 10: 265–326.

135 Bixler EO, Vgontzas AN, Lin H-M, *et al.* Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med* 2001; 163: 608–613.

136 Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care* 2003; 167: 1181–1185.

137 Shahar E, Redline S, Young T, *et al.* Hormone replacement therapy and sleep-disordered breathing. *Am J Respir Crit Care Med* 2003; 167: 1186–1192.

138 Gambacciani M, Ciapono M, Cappagli B, De Simone L, Orlandi R, Genazzani AR. Prospective evaluation of body weight and body fat distribution in early postmenopausal women with an without hormonal replacement therapy. *Maturitas* 2001; 39: 125–132.

139 Popovic RM, White DP. Upper airway muscle activity in normal women: influence of hormonal status. *J Appl Physiol* 1998; 84: 1055–1062.

140 Robinson RW, Zwillich CW. The effects of drugs on breathing during sleep. *Clin Chest Med* 1985; 6: 603–614.

141 Regensteiner JG, Woodard WD, Hagerman DD, *et al.* Combined effects of female hormones and metabolic rate on ventilatory drives in women. *J Appl Physiol* 1989; 66: 808–813.

142 Bayliss DA, Millhorn DE. Central neural mechanisms of progesterone action: application to the respiratory system. *J Appl Physiol* 1992; 73: 393–404.

143 Moore LG, McCullough RE, Weil JV. Increased HVR in pregnancy: relationship to hormonal end metabolic changes. *J Appl Physiol* 1987; 62: 158–163.

144 Hannhart B, Pickett CK, Weil JV, Moore LG. Influence of pregnancy on ventilatory and carodtid body neural output responsiveness to hypoxia in cats. *J Appl Physiol* 1989; 67: 797–803.

145 Zhou XS, Shahabuddin S, Zahn BR, Babdock MA, Badr MS. Effect of gender on the development of hypocapnic apnea/hypopnea during NREM sleep. *J Appl Physiol* 2000; 89: 192–199.

146 Jordan AS, Eckert DJ, Catcheside PG, McEvoy RD. Ventilatory response to brief arousal from non-rapid eye movement sleep is greater in men than in women. *AJRCCM* 2003; 168: 1512–1519.

147 Jordan AS, McEvoy RD, Edwards JK, *et al.* The influence of gender and upper airway resistance on the ventilatory response to arousal in obstructive sleep apnoea in humans. *J Physiol* 2004; 558: 993–1004.

148 Rowley JA, Zhou XS, Diamond MP, Badr MS. The determinants of the apnea threshold during NREM sleep in normal subjects. *Sleep* 2006; 29: 16–18.

149 Block AJ, Wynne JW, Boysen PG, Lindsey S, Martin C, Cantor B. Menopause, medroxyprogesterone and breathing during sleep. *Am J Med* 1981; 70: 506–510.

150 Pickett CK, Regensteiner JG, Woodard WD, Hagerman DD, Weil JV, Moore LG. Progestin and estrogen reduce sleep-disordered breating in postmenopausal women. *J Appl Physiol* 1989; 66: 1656–1661.

151 Cistulli PA, Barnes DJ, Grunstein RR, Sullivan CE. Effect of short term hormone replacement in the treatment of obstructive sleep apnoea in postmenopausal women. *Thorax* 1994; 49: 699–702.

152 Collop NA. Medroxyprogesterone acetate and ethanol-induced exacerbation of obstructive sleep apnea. *Chest* 1994; 106: 792–799.

153 Keefe DL, Watson R, Naftolin F. Hormone replacement therapy may alleviate sleep apnea in menopausal women: a pilot study. *Menopause* 1999; 6: 196–200.

154 Manber R, Kuo TF, Cataldo N, Colrain IM. The effects of hormone replacement therapy on sleep-disordered breathing in postmenopausal women: a pilot study. *Sleep* 2003; 26: 163–168.

155 Wesström J, Ulfberg J, Nilsson S. Sleep apnea and hormone replacement therapy: a pilot study and a literature review. *Acta Obstet Gynecol Scand* 2005; 84: 54–57.

156 Saaresranta T, Polo-Kantola P, Rauhala E, Polo O. Medroxyprogesterone in postmenopausal females with partial upper airway obstruction during sleep. *Eur Respir J* 2001; 18: 989–995.

157 Polo-Kantola P, Rauhala E, Helenius H, Erkkala R, Irjala K, Polo O. Breathing during sleep in menopause: a randomized, controlled, cross-over trial with estrogen therapy. *Obstet Gynecol* 2003; 102: 68–75.

158 Saaresranta T, Aittokallio T, Polo-Kantola P, Helenius H, Polo O. Effect of medroxyprogesterone on inspiratory flow shapes during sleep in postmenopausal women. *Respir Physiol Neurobiol* 2003; 134: 131–143.

159 Greiser CM, Greiser EM, Dören M. Menopausal hormone therapy and risk of breast cancer: a meta-analysis of epidemiological studies and randomized controlled trials. *Hum Reprod Update* 2005; 11: 561–573.

160 Weil JV, Zwillich CW. Control of breathing in endocrine and metabolic disorders and in obesity. *In*: Altose MD, Kawakami Y, eds. Control of Breathing in Health and Disease. New York, NY, Marcel Dekker, 1999; pp. 581–607.

161 Bardwell WA, Moore P, Ancoli-Israel S, Dimsdale JE. Fatigue in obstructive sleep apnea: driven by depressive symptoms instead of apnea severity? *Am J Psychiatry* 2003; 160: 350–355.

162 Black JA, Brooks SN, Nishino S. Narcolepsy and syndromes of primary excessive daytime somnolence. *Semin Neurol* 2004; 24: 271–282.

163 Veasey SC, Davis CW, Fenik P, *et al.* Long-term intermittent hypoxia in mice: protracted hypersomnolence with oxidative injury to sleep-wake brain regions. *Sleep* 2004; 27: 194–201.

164 Zhan G, Serrano F, Fenik P, *et al.* NADPH oxidase mediated hypersomnolence and brain oxidative injury in a murine model of sleep apnea. *AJRCCM* 2005; 172: 921–929.

165 Wilson SJ, Bailey JE, Alford C, Weinstein A, Nutt DJ. Effects of 5 weeks of administration of fluoxetine and dothiepin in normal volunteers on sleep, daytime sedation, psychomotor performance and mood. *J Psychopharmacol* 2002; 16: 321–331.

166 Robinson GV, Pepperell JC, Davies RJ, Stradling JR. Caffeine levels following treatment of obstructive sleep apnoea. *Thorax* 2003; 58: 801–802.

167 Boutrel B, Koob GF. What keeps us awake: the neuropharmacology of stimulants and wakefulness-promoting medications. *Sleep* 2004; 27: 1181–1194.

168 Bastuji H, Jouvet M. Successful treatment of idiopathic hypersomnia and narcolepsy with modafinil. *Prog Neuro-Psychopharmacol Biol Psychiat* 1988; 12: 695–700.

169 Billiard M, Besset A, Montplaisir J, *et al.* Modafinil: a double-blind multicentric study. *Sleep* 1994; 17: S107–S112.

170 Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. *Ann Neurol* 1998; 43: 88–97.

171 Lin JS, Roussel B, Akaoka H, Fort P, Debilly G, Jouvet M. Role of catecholamines in the modafinil and amphetamine induced wakefulness, a comparative pharmacological study in the cat. *Brain Res* 1992; 591: 319–326.

172 Lin JS, Hou Y, Jouvet M. Potential brain neuronal targets for amphetamine-, methylphenidate-, and modafinil-induced wakefulness, evidenced by c-fos immunocytochemistry in the cat. *Proc Natl Acad Sci USA* 1996; 93: 14128–14133.

173 Arnulf I, Homeyer P, Garma L, Whitelaw WA, Derenne JP. Modafinil in obstructive sleep apnea–hypopnea syndrome: a pilot study in 6 patients. *Respiration* 1997; 64: 159–161.

174 Kingshott RN, Vennelle M, Coleman EL, Engleman HM, Mackay TW, Douglas NJ. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of residual excessive daytime sleepiness in the sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 2001; 163: 918–923.

175 Pack AI, Black JE, Schwartz JR, Matheson JK. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. *Am J Respir Crit Care Med* 2001; 164: 1675–1681.

176 Schwartz JR, Hirshkowitz M, Erman MK, Schmidt-Nowara W. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea: a 12-week, open-label study. *Chest* 2003; 124: 2192–2199.

177 Black JE, Hirshkowitz M. Modafinil for treatment of residual excessive sleepiness in nasal continuous positive airway pressure-treated obstructive sleep apnea/hypopnea syndrome. *Sleep* 2005; 28: 464–471.

178 Dinges DF, Weaver TE. Effects of modafinil on sustained attention performance and quality of life in OSA patients with residual sleepiness while being treated with nCPAP. *Sleep Med* 2003; 4: 393–402.

179 Guilleminault C, Philip P. Tiredness and somnolence despite initial treatment of obstructive sleep apnea syndrome (what to do when an OSAS patient stays hypersomnolent despite treatment). *Sleep* 1996; 19: Suppl. 9, S117–S122.

180 Series F, Series I, Cormier Y. Effects of enhancing slow-wave sleep by gamma-hydroxybutyrate on obstructive sleep apnea. *Am Rev Respir Dis* 1992; 145: 1378–1383.

181 Lin JS, Sakai K, Jouvet M. Hypothalamo-preoptic histaminergic projections in sleep-wake control in the cat. *Eur J Neurosci* 1994; 6: 618–625.

182 Parmentier R, Ohtsu H, Djebbara-Hannas Z, Valatx JL, Watanabe T, Lin JS. Anatomical, physiological, and pharmacological characteristics of histidine decarboxylase knock-out mice: evidence for the role of brain histamine in behavioral and sleep–wake control. *J Neurosci* 2002; 22: 7695–7711.

183 Hancock AA. The challenge of drug discovery of a GPCT target: analysis of preclinical pharmacology of histamine H3 antagonists/inverse agonists. *Biochem Pharmacol* 2006; 71: 1103–1113.