Non-sleepy obstructive sleep apnoea: to treat or not to treat?

Nejat Altintas[1] and Renata L. Riha[2,3]

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Affiliations: [1]Pulmonary and Sleep Medicine, Namik Kemal University, Tekirdag, Turkey. [2]Dept of Sleep Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK. [3]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK.

Correspondence: Renata L. Riha, Dept of Sleep Medicine, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK. E-mail: rlriha@hotmail.com

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ABSTRACT Non-sleepy obstructive sleep apnoea (OSA) is thought to have a prevalence of around 20–25% in industrialised countries. However, the question of whether it should be routinely treated or not is controversial. This review collates the results from recent randomised controlled trials addressing OSA and examines whether treating the condition leads to improvements in quality of life and reduced cardiometabolic dysfunction, comorbidities generally attributed to untreated obstructive sleep apnoea/hypopnoea syndrome.

Introduction

Success in treating any illness is predicated on the extent to which pain, suffering and the risk of future disability can be swiftly and effectively abolished. The prevention of illness is a more complex matter, but its success is more likely if the preventive strategies employed are simple and the evidence for them clear, *e.g.* when a patient is prescribed pills for hypertension to reduce the risk of stroke.

The same cannot be said for the treatment of obstructive sleep apnoea/hypopnoea syndrome (OSAHS). With daytime sleepiness as the major hallmark of the disorder, treatment to reduce the apnoeas and hypopnoeas occurring during sleep is neither simple nor straightforward. Treatment is highly dependent on self-management and most frequently comprises nightly use of either continuous positive airway pressure (CPAP) or a mandibular repositioning device.

Long-term adherence to CPAP is one of the greatest stumbling blocks in the treatment of OSAHS, with rates ranging from 40% to 60% [1–3]. This rate relates to cohorts of patients who have self-selected by

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their attendance at sleep disorder clinics. The evidence for successful prevention of long-term complications of untreated OSAHS, which are considered to comprise metabolic dysregulation, hypertension, driving risk and cognitive decline, even in those who are highly symptomatic, is currently moderate at best and afflicted by bias as well as problems with statistical modelling, the population examined and standardised definitions [4, 5].

The evidence for successful treatment of asymptomatic obstructive sleep apnoea (OSA) is also not strong [6]. This article aims to synthesise our current understanding of what comprises OSA, as well as the short- and long-term trials that have assessed the effects of treatment on any associated comorbidities.

Definitions of sleep disordered breathing

OSAHS is the commonest form of sleep disordered breathing within industrialised communities, affecting at least 2–7% of the middle-aged population [7, 8]. OSAHS is defined as the occurrence of disordered breathing during sleep, characterised by objective measures of recurrent apnoeas and hypopnoeas, resulting in symptoms of daytime sleepiness and possible cognitive impairment.

The current "gold standard" for treating moderate-to-severe OSAHS is CPAP, which comprises mechanical splinting of the airways using compressed air delivered through a nasal or full-face mask worn during sleep. [7].

The objective metric of OSA is the apnoea–hypopnoea index (AHI), which has been subject to a variety of definitions over the decades [8]. The third edition of the International Classification of Sleep Disorders (ICSD-3) [9], for instance, encompasses a very broad definition of OSAHS, defining it as: 1) an AHI >5 events·h^{-1} of sleep with one or more symptoms (*e.g.* sleepiness, fatigue, insomnia, snoring) or an associated medical or psychiatric disorder (*e.g.* hypertension, coronary artery disease, atrial fibrillation); or 2) an AHI >15 events·h^{-1} of sleep without symptoms or associated conditions. The implication of these definitions is that OSA should be treated, since the daytime symptoms are being driven entirely and exclusively by the disturbed breathing during sleep. Currently, however, there is little evidence to support this argument, since definitions of OSAHS are derived from two components rated separately and very differently, namely severity of AHI and daytime sleepiness [8]. Indiscriminate application of the ICSD-3 criteria to data from large community-based cohorts results in 50–70% of the population being defined as having OSAHS [10]. This is clearly not the case.

When polysomnography (PSG) is used to diagnose sleep apnoea, OSAHS is defined as mild (AHI 5–15 events·h^{-1}), moderate (AHI 15–30 events·h^{-1}) or severe (AHI >30 events·h^{-1}) [11]. This does not account for age- or sex-related changes in sleep disordered breathing and there are few population-specific, normative data available [7, 8].

According to ICSD-3 [9], excessive daytime sleepiness (EDS) is defined as the inability to stay awake and alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep. Pathological sleepiness has been found to occur in 7–13% of the general population in large surveys and in 20–25% of a primary care population [8, 12]. Men and women appear to be equally affected [13]. One review estimated that 42% of all sleepiness was likely to be secondary to a medical or psychiatric disorder rather than a sleep disorder *per se* [13]. However, up to 25–50% of OSAHS patients do not report subjective tiredness or sleepiness [14].

Quantifying EDS is difficult. The most commonly used scale worldwide is the Epworth sleepiness scale [15], which has numerous limitations and the subjective nature of which has not been shown to correlate with objective measures of sleepiness [16]. An ESS score of $\geqslant$11 out of 24 is considered to indicate EDS in populations with and without OSA [8]. Objective measures to quantify sleepiness, though available, are not readily applicable to everyday clinical practice and most are utilised in the assessment of ability to drive [8].

Thus, definitions of OSAHS and OSA are dependent on the technical acquisition of electrophysiological signals, fluctuating scoring definitions and somewhat arbitrary definitions of sleepiness.

Epidemiology of OSA

The prevalence of OSA in adults worldwide is currently estimated to be 938 million people, nearly 10 times greater than previous estimates [17].

The most frequently cited paper on the topic showed that 24% of men (n=325) and 9% of women (n=250) had an AHI of >5 events·h^{-1} of sleep [18]. However, when sleepiness was factored in as causally related to the AHI, the prevalence fell to 4% in men and 2% in women. Several population prevalence studies since then have been analysed with the resultant mean (range) prevalence of OSA found to be 27.3% (9–86%) and 22.5% (3.7–63.7%) in men and women, respectively, and the mean prevalence of

OSAHS to be 6% (3–18%) and 4% (1–17%) in men and women, respectively [19]. Thus, OSA without self-reported sleepiness is almost three times as common in men and women as OSAHS. The big question remains: is OSA detrimental to health?

Is there a non-sleepy OSA phenotype?

With the prevalence of non-sleepy OSA being so high within the community, numerous studies have been undertaken over the last two decades to determine why some people with OSA develop diurnal symptoms related to nocturnal sleep disordered breathing and others do not. Additionally, sleepiness has been associated with higher levels of cardiovascular and metabolic comorbidity and many trials have attempted to ascertain whether CPAP treatment leads to improved outcomes, apart from improving quality of life primarily by reducing EDS [5, 20, 21]. Attempts at phenotyping OSA/OSAHS patients using presenting complaints have suggested other associations with comorbidities *e.g.* insomnia was more likely to herald cardiovascular abnormalities in European patients with OSA [22].

Table 1 summarises non-randomised clinical studies undertaken in an attempt to distinguish sleepy from non-sleepy OSA. Overall, the studies are heterogeneous and not directly comparable, due to technological variations and different definitions utilised. Although AHI has been shown to increase with age, the prevalence of OSAHS has not [8]. Despite differences among the studies, patients with OSAHS were more likely to have a higher body mass index, to be older and to have greater metabolic dysfunction than those with OSA without EDS [36, 37]. Whether OSA carries the same prognosis and symptom burden long term as the lack of any sleep disordered breathing and lack of sleepiness has never been formally studied. Natural history studies of sleep disordered breathing, as typified by the first paper to publish such observations in 2005 [38], suggest that in those with "mild" OSA and snoring, there is no significantly increased risk of mortality and morbidity compared to "normal" controls.

Treating OSA

CPAP therapy has a long history of generally poor adherence, which has been attributed to numerous factors, ranging from severity of the AHI, perceived benefit, personality of the patient, interface issues and type of machine [39, 40].

The seminal paper by Weaver *et al.* [41] examining the minimum duration per night of CPAP usage in 149 patients with severe OSAHS found that 4 h·night^{-1} led to a reduction in self-reported sleepiness, 6 h·night^{-1} led to improvement in objective sleepiness and 7.5 h·night^{-1} led to improvement in functional status. In terms of optimal adherence to CPAP for improving cardiovascular symptoms, the evidence is less clear. A meta-analysis conducted in 2007 of 12 trials (572 patients) suggested that there was a mean reduction in blood pressure for every 1 h of increased use of CPAP per night [42]. However, further studies, including a meta-analysis published in 2012, suggested that sleepy patients benefitted most from CPAP when self-reported sleepiness (using the ESS) fell [43].

Lastly, even with adequate compliance, many patients with a moderate-to-severe AHI will still complain of post-CPAP sleepiness [44, 45]. This can also give rise to a reduction in long-term adherence and has been the subject of numerous studies and troubleshooting guidelines [46]. The previous duration and severity of OSA and its impact on physiological functions may not be entirely reversible [47–49], or the sleepiness may be due to other factors, physical or psychological, which have not been simultaneously addressed.

More than 40 randomised controlled trials investigating the effects of CPAP on blood pressure in OSAHS have demonstrated a modest reduction in blood pressure, especially in those patients with resistant hypertension [50]. Other randomised controlled trials have shown that CPAP use in OSAHS can improve surrogate markers of cardiovascular and metabolic health, *e.g.* endothelial function, insulin sensitivity and cardiac function [51, 52]. However, the evidence has not been as consistent for OSA without sleepiness.

Results from a meta-analysis of randomised controlled trials published in 2016 [53], examining the impact of CPAP on patients with non-sleepy OSA, found minimal overall benefit on subjective sleepiness, systolic blood pressure or cardiovascular risk. Six published studies were included [54–59], as well as a seventh study [60] which incorporated and re-analysed data from a previously published dataset [56]. In total, data from 1541 patients were reviewed. The studies were published between 2001 and 2016 from sleep medicine centres in Spain, Canada, Great Britain and Sweden. Inclusion criteria were based on an AHI of $\geqslant$15 events·h^{-1} of sleep, an oxygen desaturation index (ODI) of 4% from baseline >10 events·h^{-1} of sleep, or an ODI >7.5 events·h^{-1} of sleep. Lack of sleepiness was defined as an ESS score of $\leqslant$10 out of 24 in all studies. The percentage of men in these studies ranged from 76% to 91%; the mean±SD age of the patients ranged from 53.1±2.2 years to 66±8.3 years and their body mass indexes ranged from 28.5±3.6 kg·m^{-2} to 33.2±5.3 kg·m^{-2}. CPAP use was recorded in four studies with average overall usage ranging from 2.65±0.73 h·night^{-1} to 6±1.7 h·night^{-1} and study duration from 4 weeks to 4.75 years. CPAP did not

TABLE 1 Studies examining sleepy and non-sleepy obstructive sleep apnoea patients with respect to demographic, sleep and comorbidity variables

First author [ref.]	Demographic and medical data				Polysomnographic data			
	Variable	Patients with EDS	Patients without EDS	p-value	Variable	Patients with EDS	Patients without EDS	p-value
Kapur [23]	Subjects n	510	615		Subjects n	510	615	
	Age years	63.7±62.0	65.7±66.0	<0.001	AHI events·h^{-1}	31.6±25.6	28.6±23	<0.01
	BMI kg·m^{-2}	32.0±31.1	30.8±29.9	<0.01	AHI during REM events·h^{-1}	39.0±38	36.6±34.9	<0.05
	Respiratory disease %	16.8	9.3	<0.001	AHI during NREM events·h^{-1}	29.5±24.3	26.5±21.4	<0.05
	Asthma %	10.3	5.5	<0.01	CT90 %	13.0±5.9	9.5±4.4	<0.01
	COPD %	10.5	5.1	<0.01	Mean O_2 during REM %	91.6±92.5	92.4±92.9	<0.01
	Sedative use %	11.1	7.0	<0.05	Mean O_2 during NREM %	93.1±93.4	93.4±93.6	<0.05
	Habitual snoring %	77.1	62.0	<0.001	Minimum O_2 during REM %	78.9±80	79.9±81.0	NS
	Awakening with leg cramps %	17.7	8.1	<0.001	Minimum O_2 during NREM %	80.5±83	81.5±83.0	NS
	Not getting enough sleep %	35.6	8.8	<0.001	TST min	341.7±344.5	341.9±349.0	NS
	Trouble falling asleep %	17.1	10.2	<0.01	Arousal index	28.2±25.4	27.4±25.4	NS
	Waking up too early %	24.0	11.8	<0.001	Sleep efficiency %	79.5±82	79.2±82.7	NS
					Sleep stage %			
					Stage 1	6.5±5.6	6.5±5.5	NS
					Stage 2	60.2±60.9	60.3±60.6	
					Stage 3/4	15.1±12.7	14.7±13.2	NS
					REM	18.1±18.5	18.5±18.6	NS
Mediano [24]	Subjects n	23	17		Subjects n	23	17	
	Age years	49±6	50±9	NS	AHI events·h^{-1}	62.0±18.0	60.0±20.0	NS
	BMI kg·m^{-2}	33±5	31±6	NS	Apnoea duration s	29±8	22±7	0.008
	Awake S_{pO_2} %	96±1	96±1	NS	Minimum O_2 saturation	87±6	90±5	0.01
	ESS score	17±3	5±2	<0.001	Mean O_2 saturation	69±12	79±8	0.002
	MSLT score min	4±1	16±3	<0.001	Arousal index	65±20	60±24	NS
					Sleep latency min	11±16	18±18	0.05
					Sleep efficiency	90±7	81±13	0.04
					Sleep stage %			
					Stage 1/2	81±12	71±11	NS
					Stage 3/4	6±8	8±5	NS
					REM	13±6	14±8	NS
Roure [25]	Subjects n	1649	1233		Subjects n	1649	1233	
	Age years	51±12	54±13	<0.0001	AHI events·h^{-1}	36±27	33±25	0.005
	BMI kg·m^{-2}	31±6	31±6	NS	Minimum O_2 saturation	78±12	79±11	0.013
	Current smoker %	28	24	0.03	Mean O_2 saturation	92±5	92±4	0.1
	Male %	85	85	NS	TST min	338±67	325±65	0.007
	Awake S_{aO2}	96±1	96±1	NS	Arousal index	37±31	33±23	<0.0001
	ESS score	15±3	7±3	<0.0001	Sleep latency min	21±27	28±31	<0.0001
					Sleep efficiency %	79±22	72±31	<0.0001
					Sleep stage %			
					Stage 1/2	83±14	86±11	0.007
					Stage 3/4	11±13	8±10	0.018
					REM	5±4	5±4	0.9

Continued

TABLE 1 Continued

First author [ref.]	Demographic and medical data				Polysomnographic data			
	Variable	Patients with EDS	Patients without EDS	p-value	Variable	Patients with EDS	Patients without EDS	p-value
Oksenberg [26]	Subjects n	327	242		Subjects n	327	242	
	Age years	54.4±10.7	57.0±10.7	0.008	AHI events·h^{-1}	67.2±21.6	57.1±18.3	0.0001
	BMI kg·m^{-2}	34.3±5.5	33.0±5.2	0.009	Arousal index	35.0±23.0	24.2±17.6	0.0001
	Male %	85.3	83.5	NS	Minimum S_{aO2} during REM %	67.5±16.1	74.3±13.4	0.0001
	Hypertension %	46	51	0.033	Minimum S_{aO2} NREM %	77.1±10.1	80.5±7.6	0.0001
					Arousal index	65.5±21.3	58.0±20.5	0.0001
					Sleep latency min	8.6±10.1	12.3±18.9	0.014
					Sleep efficiency	83.2±10.0	82.2±10.5	NS
					Sleep stage %			
					Stage 3/4	10.9±9.0	14.5±8.4	0.0001
					REM	17.2±5.8	17.1±6.0	NS
Montemurro [27]	Subjects n	31	60		Subjects n	31	60	
	Age years	54.7±12.0	57.5±13	0.328	AHI events·h^{-1}	46.9±15.2	56.7±19.9	0.018
	BMI kg·m^{-2}	31.0±5.8	33.1±6.1	0.117	Minimum S_{aO2} %	78.5±9.1	75.5±11.5	0.208
	Male %	83	75	0.427	Mean S_{aO2} %	94.6±2.1	93.4±2.5	0.021
	ESS score	13±2.2	5.8±(2.6	<0.001	TST min	295.0±67.5	304.2±76.7	0.578
					Arousal index	41.4±15.2	50.6±19.1	0.022
					Sleep latency min	12.1±14.1	15.4±15.6	0.326
					Sleep efficiency %	72.7±14.5	73.5±16.6	0.827
					Sleep stage %			
					Stage 1	15.7±10.0	12.7±7.5	0.112
					Stage 2	61.2±14.0	65.1±11.6	0.161
					Stage 3	11.1±9.9	9.4±7.8	0.365
					REM	12.9±5.7	12.7±7.3	0.878
Bravo [28]	Subjects n	22	50		Subjects n	22	50	
	Age years	51.3±1.4	52.3±2.4	NS	AHI events·h^{-1}	53.1±3.9	48.9±3.3	NS
	BMI kg·m^{-2}	33.3±1.0	30.9±1.4	NS	Mean S_{aO2} %	86.4±1.2	89.4±1.7	NS
	Current smoker %	42.8%	40.9%	NS				
	Hypertension %	57.1%	68.2%	NS				
	ESS score	16.8±0.5	5.3±0.8	<0.001				
	Serum level of							
	P-selectin ng·mL^{-1}	129.1±7.6	114.1±4.8	NS				
	ICAM-1 ng·mL^{-1}	312.7±24.8	263.0±11.0	0.075				
	TNF-α pg·mL^{-1}	0.82±0.11	0.89±0.37	NS				
	IL-6 pg·mL^{-1}	3.02±0.3	2.44±0.37	NS				
	8-iso-PGF2α pg·mL^{-1}	730.5±74.3	584.0±66.1	0.051				
Koutsourelakis [29]	Subjects n	354	561		Subjects n	354	561	
	Age years	53.6±12.8	49.6±14.0	<0.001	RDI events·h^{-1}	44.9±33.8	20.9±22.7	<0.001
	BMI kg·m^{-2}	34.0±7.8	30.2±7.0	<0.001	Minimum S_{aO2}%	75.6±11.1	82.7±8.6	<0.001
	Male %	75.7	70.1	NS	Mean S_{aO2}%	91.3±4.7	93.6±4.8	<0.001
	Current smoker %	39.8	41.2	NS	TST min	261.3±76.6	282.3± 73.0	<0.001
	Alcohol use %	20.3	12.5	<0.001	Sleep latency min	21.2±24.3	24.4±32.4	NS
	COPD %	17.4	2.0	<0.001	Sleep efficiency %	88.2±12.9	89.4±34.5	NS
	Asthma %	4.1	2.6	NS	Sleep stage %			
	Stroke %	8.2	0	<0.001	Stage 1	5.2±5.8	4.2±4.7	<0.01
	Diabetes %	21.2	3.9	<0.001	Stage 2	80.3±12.5	78.5±12.6	NS
	Depression %	15.8	2.0	<0.001	Stage 3	2.4±7.6	4.0±8.4	<0.01
	Ischaemic heart disease %	26.0	3.9	<0.001	REM	11.8±8.0	12.7±7.7	NS
	Hypertension %	47.5	25.7	<0.001				
Sun [30]	Subjects n	32	48		Subjects n	32	48	
	Age years	42.97±10.33	45.17±12.56	0.414	AHI events·h^{-1}	60.92±19.24	33.68±22.71	0.001
	BMI kg·m^{-2}	27.94±3.62	25.92±4.13	0.027	Minimum S_{aO2}%	54.06±21.22	73.10±14.97	0.001
	Awake S_{O2} %	93.38±4.35	95.92±1.90	0.001	Mean S_{aO2}%	90.06±5.57	94.56±4.15	0.001
	ESS score	16.53±3.79	5.29±3.15	0.001	TST min	474.48±57.60	406.23±75.75	0.001
	MSLT score min	3.56±1.04	14.67±3.02	0.001	Arousal index	56.25±23.64	28.93±16.95	0.001

Continued

TABLE 1 Continued

First author [ref.]	Demographic and medical data				Polysomnographic data			
	Variable	Patients with EDS	Patients without EDS	p-value	Variable	Patients with EDS	Patients without EDS	p-value
					Sleep latency min	8.75±9.50	21.05±19.80	0.001
					Sleep efficiency %	90.40±7.23	83.61±12.27	0.003
					Sleep stage %			
					Stage 1	33.66±23.25	22.70±26.80	0.026
					Stage 2	44.58±19.08	50.78±19.17	0.160
					Stage 3	10.06±10.19	13.68±8.05	0.081
					REM	11.69±7.33	12.83±5.93	0.447
Seneviratne [31]	Subjects n	170	25		Subjects n	170	25	
	Age years	44.4±11	52.7±8.8	<0.005	RDI events·h^{-1}	37.1±24.9	25.9±18.7	0.038
					Minimum S_{aO2}%	71.8±14.9	77.7±12.6	0.053
					Arousal index	34.9±23.5	32.3±49.7	0.032
					PLM index	4.4±16.3	1.7±5.6	0.587
					Arousals with PLM	8.3±23.6	1.5±5.2	0.398
					Degree of snoring	2.4±0.7	1.9±0.6	<0.005
					Sleep efficiency %	76.0±14.6	86.7±10.3	<0.005
					Sleep stage %			
					Stage 3	8.7±7.4	8.9±7.8	0.950
					REM	13.0±5.9	13.1±7.70	0.802
Wang [32]	Subjects n	229	109		Subjects n	229	109	
	Age years	48.80±12.70	53.00±12.30	0.002	AHI events·h^{-1}	42.00 (5.00–117.40	32.40 (5.00–94.80)	0.072
	BMI kg·m^{-2}	28.00 (19.40–43.90)	27.10 (15.60–40.10)	0.090	CT90 %	14.20 (0–84.12)	8.66 (0–97.55)	0.047
	Male %	80	72	0.104	Minimum O_2 %	74.00 (60.00–95.00)	79.00 (60.00–95.00)	0.095
	ESS score	13±9–24	6±0–8	<0.001	Mean O_2 %	92.00 (74.00–98.00)	93.00 (62.00–97.00)	0.019
	Bedtime SBP mmHg	125.64±14.96	125.18±12.87	0.784	ODI	38.40 (0.9–161.40)	35.10 (4.00–99.20)	0.405
	Bedtime DBP mmHg	82.73±10.53	80.07±9.04	0.019				
	Morning SBP mmHg	131.52±17.12	130.22±14.73	0.505				
	Morning DBP mmHg	88.45±12.30	84.59±9.52	0.002				
	Bedtime MAP mmHg	97.04±10.94	95.30±8.82	0.124				
	Morning MAP mmHg	102.81±12.61	99.80±9.48	0.018				
	Waking up with dry mouth %	66.5	56.7	0.060				
Barcelò [33]	Subjects n	22	22		Subjects n	22	22	
	Age years	49±6	50±5	0.142	AHI events·h^{-1}	52±19	48±16	0.396
	BMI kg·m^{-2}	32±3	31±4	0.230	Minimum O_2 %	69±12	81±8	0.010
	Current smoker %	48	40	NS	Mean O_2 %	86±6	90±5	0.040
	ESS score	16±3	4±3	<0.001	Arousal index	65±19	62±25	0.732
	MSLT score min	5±3	15±3	NS				
	Glucose mg·dL^{-1}	115±19	103±20	0.032				
	HDLc mg·dL^{-1}	46±10	56±11	0.002				
	HOMA index	4.3±2.4	2.3±1.8	<0.001				
	Insulin mU·mL^{-1}	15.2±7.6	8.6±4.8	<0.001				
Nena [34]	Subjects n	25	25		Subjects n	25	25	
	Age years	43.2±9.5	46.3±10.5	0.269	AHI events·h^{-1}	53.1±16.3	50.1± 18.3	0.550
	BMI kg·m^{-2}	37.1±6.3	34.8±6.5	0.218	CT90 %	35±25.1	23.3±16	0.055
	Male %	88	84	1.000	Minimum O_2 %	77.4±6.1	77.8±8.1	0.845
	ESS score	16.4±3.7	6.2±2.9	<0.001	Mean O_2 %	88.8±4.3	90.4±1.6	0.079
	Glucose mg·dL^{-1}	102.9±16.9	94.1±13.1	0.045	ODI	56.4±18.7	48.7±20.5	0.170
	HOMA index	5.1±4.3	3±1.6	0.027				
	Insulin µIU·mL^{-1}	19.7±14.3	11.5±5.6	0.012				
Huang [35]	Subjects n	119	56		Subjects n	119	56	
	Age years	44.2±10.4	42.8±12.2	0.438	AHI events·h^{-1}	57.9 (43.8–73.0)	56.1 (44.9–65.2)	0.336

Continued

TABLE 1 Continued

First author [ref.]	Demographic and medical data				Polysomnographic data			
	Variable	Patients with EDS	Patients without EDS	p-value	Variable	Patients with EDS	Patients without EDS	p-value
	BMI kg·m^{-2}	27.95±4.1	26.4±4.9	0.032	Min O_2 %	71.0 (60.0–82.0)	80.0 (65.00–86.0)	0.019
	Current smoker %	39.5	37.5	0.869	Mean O_2 %	92.0 (88.0–95.0)	95.0 (92.75–96.0)	<0.001
	ESS score	15.4±3.8	6.6±2.2	<0.001	ODI	27.6 (12.1–50.0)	42.9 (16.1–61.9)	0.071
	Central obesity	89.9	69.6	<0.001				
	Hypertriglyceridemia %	77.3	14.3	<0.001				
	Metabolic syndrome %	78.2	28.6	<0.001				
	Metabolic score	3.2±0.9	1.9±1.1	<0.001				

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. EDS: excessive daytime sleepiness; BMI: body mass index; ESS: Epworth sleepiness scale; MSLT: multiple sleep latency test; S_{aO_2}: arterial oxygen saturation; S_{pO_2}; arterial oxygen saturation measured by pulse oximetry; RDI: respiratory disturbance index; ICAM: intercellular adhesion molecule; TNF: tumour necrosis factor; IGF-1: insulin-like growth factor I; IL: interleukin; PGF2α: prostaglandin F2α; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HDLc: high-density lipoprotein cholesterol; HOMA: homeostasis model assessment; AHI: apnoea–hypoapnoea index; REM : rapid eye movement; NREM : non-rapid eye movement; CT90: percentage of sleep time spent <90% oxygen saturation; TST: total sleep time; PLM: periodic leg movement; ODI: oxygen desaturation index; NS: nonsignificant.

improve ESS score overall but it did improve the AHI/ODI significantly *versus* controls (p=0.026). Diastolic blood pressure in those treated with CPAP fell on average by 0.92 mmHg (95% CI −1.39 to −0.46 mmHg; p<0.001).

Of course, there are limitations to every study. This should be borne in mind when interpreting *post hoc* analyses. BARBE *et al.* [55] reported cardiovascular risk reduction in patients who used CPAP for ⩾4 h·night^{-1}, as did PEKER *et al.* [59]. Choosing 4 h·night^{-1} usage as a cut-off appears arbitrary in the context of what is known about CPAP use as discussed above.

Two studies have examined whether reasonable adherence can be reached with CPAP in non-sleepy OSA. CAMPOS-RODRIGUEZ *et al.* [61] reported that after following 357 non-sleepy patients with an AHI ⩾20 events·h^{-1} in multiple Spanish sleep centres for a median of 4 years, 230 (64.4%) had a compliance of ⩾4 h·night^{-1}. They found that a higher AHI at baseline and the presence of hypertension were associated with better adherence. In their group of patients with coronary artery disease and OSA, LUYSTER *et al.* [62] demonstrated that the probability of remaining on CPAP at 2 years was 60% in non-sleepy patients and 77% in sleepy patients. A positive experience of using CPAP initially was a strong determinant of long-term use.

These results bring to attention the difficulties in defining EDS in these groups of patients and possibly do not account for issues with bed-partners (who may reinforce CPAP use even in the non-sleepy to control noise levels), the amount and quality of effort and input that a nurse or physician contributes to encouraging a patient to continue on CPAP, and personality. In the context of a trial, the Hawthorne effect can cause bias in both control and treatment groups not present in real life.

Finally, one trial published in 2016 is worth discussing in the context of non-sleepy OSA, although the enrolment criterion of an ESS score of ⩽15 out of 24 does not conform to the accepted definition of not being sleepy. This was the "CPAP for prevention of cardiovascular events in obstructive sleep apnoea trial" (SAVE trial) [63], which recruited a very large population (n=2717 total; aged 45–75 years) in order to examine the effects of CPAP on cardiovascular and cerebrovascular outcomes. The trial was designed to be multicentre, parallel-group and open-label, enrolling moderate to severe OSA patients with an ESS score of ⩽15 out of 24 with cardiovascular disease or cerebrovascular disease. Follow-up was for a mean of 3.7 years only. CPAP failed to protect patients from a composite death score which included heart failure, myocardial infarction, hospitalisation for unstable angina, stroke or transient ischaemic attack, compared to controls without CPAP, despite significantly reducing daytime sleepiness and improving quality of life, mood and work capacity. However, mean duration of CPAP adherence was 3.3 h·night^{-1} during follow-up.

A *post hoc* analysis [64] used latent class analysis to identify high-risk OSA clinical phenotypes. Latent class analysis identified four OSA clinical phenotypes: coronary artery disease (CAD) alone, CAD+diabetes mellitus (DM), cardiovascular disease alone and cerebrovascular disease +DM. Composite cardiovascular events were highest for the CAD+DM phenotype. The presence of diabetes in OSA patients with CAD or cardiovascular disease increased the risk of the composite outcome occurring despite treatment. However, adequate CPAP treatment (>4 h·night^{-1}) reduced cardiovascular risk in diabetic patients with OSA, with the strongest effect being seen in patients with cerebrovascular disease. Although disappointing, the results of the SAVE trial may have been subject to a number of important biases and complications. The majority of the subjects enrolled in the study were from two distinctly different ethnic groups (62%); there was a high dropout rate (83%) and high cross-over of control group patients (57 patients) into the CPAP treatment arm. For ethical reasons, patients with EDS and severe hypoxaemia (oxyhaemoglobin saturation <80% for >10% of sleep study time) were excluded, thus limiting the sample to a potentially lower-risk group, and finally, the CPAP usage rates were low. The use of CPAP for only a short part of the night may have resulted in patients missing most of their rapid eye movement (REM) sleep on treatment. REM-linked apnoeas and hypopneas are typically lengthy and are associated with greater oxyhaemoglobin desaturations and higher sympathetic tone. REM-related OSA is specifically associated with incident or recent onset hypertension and cardiovascular disease [65–67].

Discussion

Recently, a pro–con debate on whether non-sleepy, moderate to severe OSA should be treated or not has been published [6, 47].

In arguing against treating OSA indiscriminately, Vakulin *et al.* [6] pointed out that the cost of new technologies and the pressures on healthcare worldwide means that allocation of resources for any disease is dependent on the knowledge that the disorder causes significant ill health and that a high level of evidence exists to show that treatments offered are effective, cost-effective and safe. This is true for OSAHS, where sufficient evidence exists to offer treatment for symptom control. However, the evidence is not so convincing in those who have OSA. On the other hand, Ryan [47] argues that the term "asymptomatic" is likely to be misleading and that randomised controlled trials have demonstrated that, even in patients with an ESS score ⩽10 out of 24, further improvement in quality of life can occur with treatment in addition to subtle changes in endothelial function and normalisation of nocturnal blood pressure profiles. The relatively short-term follow-up in published randomised controlled studies [54–59], which are likely to be underpowered with respect to such observations, cannot address these questions. Additionally, Ryan [47] argues that there is large interindividual variability in CPAP response that may be linked to the duration of the disease prior to diagnosis, which may have resulted in irreversible tissue damage [48, 49].

CPAP adherence has been a source of contention in the studies discussed in this review and an important variable which may influence outcomes. The literature currently advocates a threshold approach to CPAP use with data overall supporting a dose–response relationship dependent on the variable or outcome being studied [39]. However, no absolute optimal adherence levels to CPAP have ever been determined [39]. Although patients with OSA have been shown to adhere to CPAP successfully, the overall rates of use after a few years fall to around 60%, worse by at least 10% in comparison to patients with OSAHS [39].

To date, phenotyping patients with non-sleepy OSA has been somewhat elusive and is likely to be unhelpful on a practical basis when the clinician is faced with each patient as an individual with their own set of particular characteristics. In this situation, extrapolation of results from short-term trials is not likely to be helpful in making long-term treatment decisions.

Conclusion

Diurnal dysfunction secondary to intermittent hypoxaemia and recurrent sympathetic arousals during the sleep period are not universal findings in sleep apnoea. However, the evidence for a direct link between untreated OSAHS and cardiometabolic consequences is considerable, even though treatment does not always fully reverse the abnormalities. The association of these abnormalities with OSA is not strong and trials reporting positive treatment effects are of short-term duration, uncontrolled or have been undertaken in very specific population cohorts. How these data are then applied on a daily basis to other populations and patients with other clinical characteristics remains the difficulty and the dilemma. Challenges in future research include the incorporation of precise, objectively assessed definitions of sleepiness, long-term follow-up, correction for age- and sex-related norms in AHI and sleepiness and adequate study power. In the future, one way of simplifying diagnostic and treatment pathways would be to classify patients as CPAP or non-CPAP responsive, irrespective of AHI and degree of sleepiness. Since sleepiness is not

always the direct result of sleep apnoea, this might form the basis for a more practical approach in our day-to-day clinical practice and help resolve some of the less soluble questions we face.

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