Investigation and management of residual sleepiness in CPAP-treated patients with obstructive sleep apnoea: the European view

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Drugs for EDS are available in the USA but were discontinued in Europe some time ago. For European sleep doctors, treatment of EDS with medication is new, while novel wake-promoting drugs have been developed and approved for clinical use in OSA patients. https://bit.ly/3u9y3Ln

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Abstract

Excessive daytime sleepiness (EDS) is a major symptom of obstructive sleep apnoea (OSA), defined as the inability to stay awake during the day. Its clinical descriptors remain elusive, and the pathogenesis is complex, with disorders such as insufficient sleep and depression commonly associated. Subjective EDS can be evaluated using the Epworth Sleepiness Scale, in which the patient reports the probability of dozing in certain situations; however, its reliability has been challenged. Objective tests such as the multiple sleep latency test or the maintenance of wakefulness test are not commonly used in patients with OSA, since they require nocturnal polysomnography, daytime testing and are expensive. Drugs for EDS are available in the United States but were discontinued in Europe some time ago. For European respiratory physicians, treatment of EDS with medication is new and they may lack experience in pharmacological treatment of EDS, while novel wake-promoting drugs have been recently developed and approved for clinical use in OSA patients in the USA and Europe. This review will discuss 1) the potential prognostic significance of EDS in OSA patients at diagnosis, 2) the prevalence and predictors of residual EDS in treated OSA patients, and 3) the evolution of therapy for EDS specifically for Europe.

Introduction

Patients often seek medical advice for excessive daytime sleepiness (EDS), which is a major symptom of obstructive sleep apnoea (OSA) [1]. Sleepiness is defined as the inability to stay awake during the day, but its clinical descriptors remain elusive in both central disorders of hypersomnolence, such as narcolepsy or idiopathic hypersomnia [2] and in OSA [3, 4]. Moreover, the pathogenesis of EDS is complex and sleep disorders are not the only cause of EDS. Insufficient sleep, diseases such as diabetes, hypothyroidism or depression, and habitual use of some medications like hypnotics are amongst the most common. Patients' symptoms may improve with OSA therapy such as continuous positive airway pressure (CPAP), but a proportion will remain sleepy [5].

Clinical evaluation of EDS can be performed by using subjective and objective tests [6]. The latter include the multiple sleep latency test (MSLT) and the maintenance of wakefulness test (MWT), which measure the propensity to fall asleep and the ability to stay awake, respectively. In patients with OSA, they are not

commonly used, since they require full nocturnal polysomnography, additional daytime testing and are expensive. Subjective EDS can be evaluated by using the Epworth Sleepiness Scale (ESS), in which the patient reports the probability of dozing off in eight different situations [7]. A score ⩾11 is considered as positive for EDS, and ⩾16 indicates severe sleepiness. The reliability and repeatability of the ESS have been recently challenged [8–10].

Some drugs used to treat EDS despite CPAP, so-called residual EDS or residual sleepiness (RES), have been available in the United States but were discontinued in Europe about 10 years ago. Therefore, for many European respiratory physicians, treatment of RES with medication represents a new scenario, since they may lack experience in pharmacologic treatment of EDS, while new wake-promoting drugs have been recently developed and approved for clinical use in OSA patients in United States and Europe. In this review, we describe why sleepiness at diagnosis may have prognostic implications, how common RES is in our OSA population and how pharmacological therapy has evolved especially in recent times. We will focus on the European perspective, but the interested reader is referred to other recent reviews published from the USA [11, 12].

EDS at diagnosis: a risk factor for poor outcome in OSA

EDS is – together with snoring, male gender and obesity – the most prominent clinical sign of OSA. Up to 50% of the patients at diagnosis present with alternative symptoms, such as insomnia and disturbed sleep [13]. However, EDS is clinically most relevant as it affects quality of life and performance in private, social, and professional activities, and increases the risk of accidents whilst driving or at work [14, 15]. Several studies addressed the question if EDS independently predicts morbidity and mortality in OSA patients, as summarised in table 1.

Empana *et al*. [16] performed a population-based multicentre prospective study in France in subjects aged ⩾65 years followed over 6 years. The majority of them reported EDS and nocturnal sleep complaints, with a prevalence of EDS during follow-up of 18.7%. This was associated with an increased risk of mortality (1.33, 95% CI 1.13–1.61) after full adjustment for risk factors.

Other studies reported that only OSA with EDS was associated with increased risk [17], whereas neither sleep-disordered breathing nor EDS alone increased all-cause mortality. In a longitudinal study in 289 patients aged >65 years without clinical signs of dementia or depression followed for 13.8 years, moderate to severe OSA (apnoea/hyponoea index (AHI) ⩾20 events·h^{-1}) with EDS was associated with a 2.3 hazard ratio (HR) of mortality (95% CI 1.5–3.6) [18].

Similarly, in a prospective study in 2320 community-dwelling elderly (mean age: 73.6 years; follow-up: 9.9 years), the sample was divided into four groups based on snoring and EDS. The HR for incident cardiovascular events was significantly increased only in patients with snoring and EDS (1.46 (95% CI 1.03–2.08)) after adjusting for demographic and clinical confounding factors [19].

EDS may also predict cardiovascular events. In 104 patients with myocardial infarction followed for 48 months and studied by ESS and polysomnography, an ESS score ⩾11 was associated with a higher risk for major cardiac events and re-infarction compared to the no EDS group (HR 2.15 (95% CI 1.08–4.18)). If EDS was associated with moderate to severe sleep-disordered breathing, the HR was 3.17 (95% CI 1.22–7.76) after adjustment for age and nadir oxygen saturation [20].

Most studies on the impact of EDS on survival focus on cardiovascular mortality. In the Cardiovascular Health Study (n=5888), EDS was the only symptom associated with mortality, incident cardiovascular morbidity, myocardial infarction and chronic heart failure (HF). After adjustment for age, the HR for mortality was 1.82 for men and 1.29 for women [21].

More recently, Mazzotti *et al*. [17] analysed OSA patients from the Sleep Heart Health Study to characterise phenotypes and assess their association with cardiovascular disease. The clinical phenotype with EDS showed a threefold higher risk of prevalent HF compared with the other phenotypes. In addition, both excessive and moderate EDS at diagnosis predicted an increased risk for incident cardiovascular disease, coronary heart disease and HF. Similar findings have been recently reported in Hispanic OSA patients [22].

Finally, some reports underlined the association of EDS and stroke, suggesting that daytime sleepiness is an independent risk factor for stroke and other cardiovascular events [23].

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TABLE 1 Studies investigating the association between excessive daytime sleepiness (EDS) and mortality and morbidity

First author, year [ref.]	Study type	Sample	Tests used	Results	Comments
Gooneratne, 2011 [18]	Longitudinal cohort	289 patients >65 years old with no dementia or depression but EDS and OSA	Observed for mean 13.8 years	Combination of AHI ⩾20 events·h^{-1} and EDS associated with 2.3 HR of mortality (95% CI 1.5–3.6)	Neither sleep disordered breathing nor EDS alone led to increased all-cause mortality PSG+, no difference in PSG parameters between sleepy and non-sleepy patients
Empana, 2009 [16]	Multicentre prospective longitudinal cohort	9294 patients >65 years old; 8269 had EDS or nocturnal sleep problems	Observed for 6 years	18.7% had EDS frequently which showed increased adjusted risk of mortality 1.3 (95% CI 1.13–1.61)	EDS was predictive of cardiovascular related mortality in snorers and non-snorers No PSG
Newman, 2000 [21]	Observational	5888 patients in a CV health study	Interview-administered questionnaire regarding sleep disturbance and CV risk	EDS had HR for mortality adjusted for age 1.82 for men, 1.29 for women	EDS was the only symptom associated with mortality, CV morbidity, MI and chronic heart failure No PSG
Mazzotti, 2019 [17]	Longitudinal cohort	1207 patients with OSA from Sleep Heart Health Study	Cluster analysis of symptom subtypes including excessive and moderate EDS	EDS subtype 3× risk of heart failure Moderate (38.5%) and excessive (16.7%) showed increased risk for CV disease, coronary heart disease and HF	EDS shows high CV risk profile compared to other symptoms subtypes No PSG
Endeshaw, 2013 [19]	Longitudinal cohort	2320 community participants	Observed for mean 9.9 years 553 developed CV events	HR 1.46 (95% CI 1.03–2.08) in snorers with EDS after adjusting for demographics and known confounders	Those without snoring and/or sleepiness had no increased CV event risk No PSG
Xie, 2018 [20]	Observational	104 post MI patients	Observed for 48 months; had PSG and ESS	ESS >11 had higher risk of major CV events and re-infarction compared with non-sleepy patients Adjusted HR 2.15 (95% CI 1.08–4.18) If moderate-to-severe OSA plus EDS, then HR 3.17 (95% CI 1.22–7.76)	Even after adjustment for CV risk factors, oxygen saturation and AHI, a significant HR for CV events remains for the excessively sleepy group PSG+, no data provided
Boden-Albala, 2012 [23]	Longitudinal cohort	Community-based study of association of stroke and EDS with 47% reporting some dozing	Observed for 5.1 years	Participants with significant dozing had increased risk of stroke, stroke plus MI or death, and all vascular deaths HR 2.74, 2.38 and 2.48	Authors concluded that EDS was an independent risk factor for stroke and CV events No PSG

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TABLE 1 Continued

First author, year [ref.]	Study type	Sample	Tests used	Results	Comments
Kasai, 2020 [24]	Observational prospective	218 patients with systolic HF	Underwent PSG then observed for mean 28 months	80 had AHI ⩾15 events·h^{-1} Low ESS (<6) associated with higher mortality than ESS >6	Worse outcomes for less sleepy group PSG+, no difference in PSG parameters between sleepy and non-sleepy patients
Ogilvie, 2018 [25]	Observational	3874 participants in Sleep Heart Health Study; AHI ⩾15 events·h^{-1} and ESS ⩾11	Incidence of CV events in the study population	EDS showed an increased risk of CV disease but not statistically significant	Large study which did not show an association Home PSG+, no data provided
Lee, 2013 [26]	Observational prospective cohort	170 patients undergoing coronary angiography	Observed for 16 months for CV events; blood lipid and intravascular ultrasound for coronary plaque assessment	ESS >10 had higher total cholesterol and LDL HR for CV events in sleepy group 3.44 (95% CI 1.01–11.72)	Sleepy patients had higher cholesterol, LDL and longer coronary stenosis as well as higher incidence of CV events No PSG
Pak, 2020 [27]	Case-controlled observational	57 sleepy participants *versus* 37 non-sleepy	C1qTNF1, adipokine, 24 h blood pressure and sleepiness (ESS)	C1qTNF1 was higher in sleepy group (β=0.41; 95% CI 0.02–0.8; p=0.04) 24 h blood pressure was also higher	Possible mechanisms for sleepiness leading to increased incidence of CV events No PSG
Taranto Montemurro, 2012 [28]	Observational	27 patients with OSA and heart failure	MSNA measured and PSG	Less sleepy patients had higher MSNA than sleepy patients (ESS ⩾6)	No association with sleepiness with an inverse relationship between ESS and MSNA PSG+, no difference in PSG parameters between sleepy and non-sleepy patients

C1qTNF1: complement C1q tumour necrosis factor-related protein 1; CV: cardiovascular; ESS: Epworth Sleepiness Scale; HF: heart failure; AHI: apnoea/hyponoea index; HR: hazard ratio; LDL: low density lipoprotein; MI: myocardial infarction; MSNA: muscle sympathetic nerve activity; OSA: obstructive sleep apnoea; PSG: polysomnography.

Although the majority of investigations reported increased cardiovascular mortality in patients with EDS, there are also negative results. In patients with systolic HF and AHI ⩾15 events·h^{-1} at polysomnography, 5-year mortality was significantly higher in patients with ESS <6 as compared to those with an ESS ⩾6 in a fully adjusted model [24]. In 3874 participants of the Sleep Heart Health Study with an AHI ⩾15 events·h^{-1} and an ESS score ⩾11 without prevalent cardiovascular disease at baseline, no significant association was found between EDS and risk of cardiovascular disease [25].

There are limited and controversial data on the possible pathogenetic mechanisms underlying the association between mortality and EDS. Lee at al. [26] performed a prospective cohort study to assess associations between coronary plaque phenotype, cardiovascular events and EDS. They measured blood lipid parameters and intravascular ultrasound for plaque evaluation in 170 patients undergoing coronary angiography. Patients with an ESS >10 had significantly higher total cholesterol and low-density-lipoprotein cholesterol. The coronary stenoses were longer and the cumulative incidence of adverse cardiovascular events during the 16-month follow-up was higher in the sleepier group. After adjustments for age and smoking habits, the HR for adverse cardiovascular events in the sleepier group was 3.44 (95% CI 1.01–11.72).

Considering other risk factors, Pak *et al*. [27] analysed the association between subjective sleepiness on the one hand and increased plasma tumour-necrosis-factor-related protein-1 (C1qTNF1), adipokines and 24 h ambulatory blood pressure on the other. C1qTNF1 was significantly higher in sleepy patients compared to those with an ESS <10. The 24 h blood pressure was significantly higher in sleepy participants as compared to nonsleepy participants.

The sympathetic nervous system plays a role in alertness, and both HF and OSA increase sympathetic nerve activity. In OSA patients with HF, an inverse relationship was found between muscle sympathetic nerve activity (MSNA) and ESS, but not with AHI, arousal index or oxygen saturation [28].

In summary, EDS is a major symptom of OSA but does not occur in all patients. Despite some conflicting findings, the majority of population-based data imply that EDS may be a marker of poor outcome, since it appears independently associated with cardiovascular morbidity and mortality. The prognostic role of persistent EDS in OSA during CPAP treatment has not been explored to date.

EDS in treated OSA patients

The most common treatment of OSA is the application of CPAP during sleep. CPAP splints the airway open and prevents occurrence of obstructive respiratory events. CPAP improves daytime sleepiness more effectively than placebo [29, 30]. A recent meta-analysis on the results of randomised control trials documented a significant reduction in subjective sleepiness, *i.e.* the ESS score, post-CPAP, whereas among objective tests changes were significant for the MWT but not for the MSLT [31]. A change in the ESS score of 2 points was considered as clinically significant, in agreement with the estimate of −2 to −3 points as the minimum clinically important difference in ESS score in treated OSA patients [32, 33].

A recent review [34] describes the complex relationship between OSA, cardiovascular risk and CPAP therapy in patients with or without EDS. It is noted that patients with severe EDS and OSA have a greater reduction in blood pressure and cardiovascular risk with CPAP than patients without EDS. This is important to bear in mind when thinking about additional treatments.

Some patients fail to improve their sleepiness after CPAP, with multiple factors possibly involved. In order to evaluate the cause and impact of the sleepiness for the patient a full sleep history by a sleep specialist must be taken (if not already available) rather than merely relying on the ESS. The history should also ask about the intensity and frequency of the sleepiness over a week as the ESS is known to vary considerably intraday and over time [35]. In addition, care should be taken when interpreting the ESS score as a patient may under or overestimate their sleepiness and have substantial misperception of effective sleepiness [36].

A step-wise approach should then be taken (see figure 1 for a guide).

First, CPAP-related problems may occur and should be carefully investigated. Suboptimal therapeutic pressure, poor mask fitting, or air leaks from the mask are common causes of persistent respiratory events, sleep fragmentation, and sleepiness during treatment. A recent meta-analysis pointed out that use of an oronasal mask was associated with incomplete resolution of OSA and poorer adherence compared to the use of a nasal mask [37]. When automatic positive airway pressure (APAP) is used, the pressure level varies according to sleep stages and position leading to the occurrence of arousals which may disturb sleep [38]. CPAP or APAP machines provide data on residual AHI and adherence to treatment. A high level of

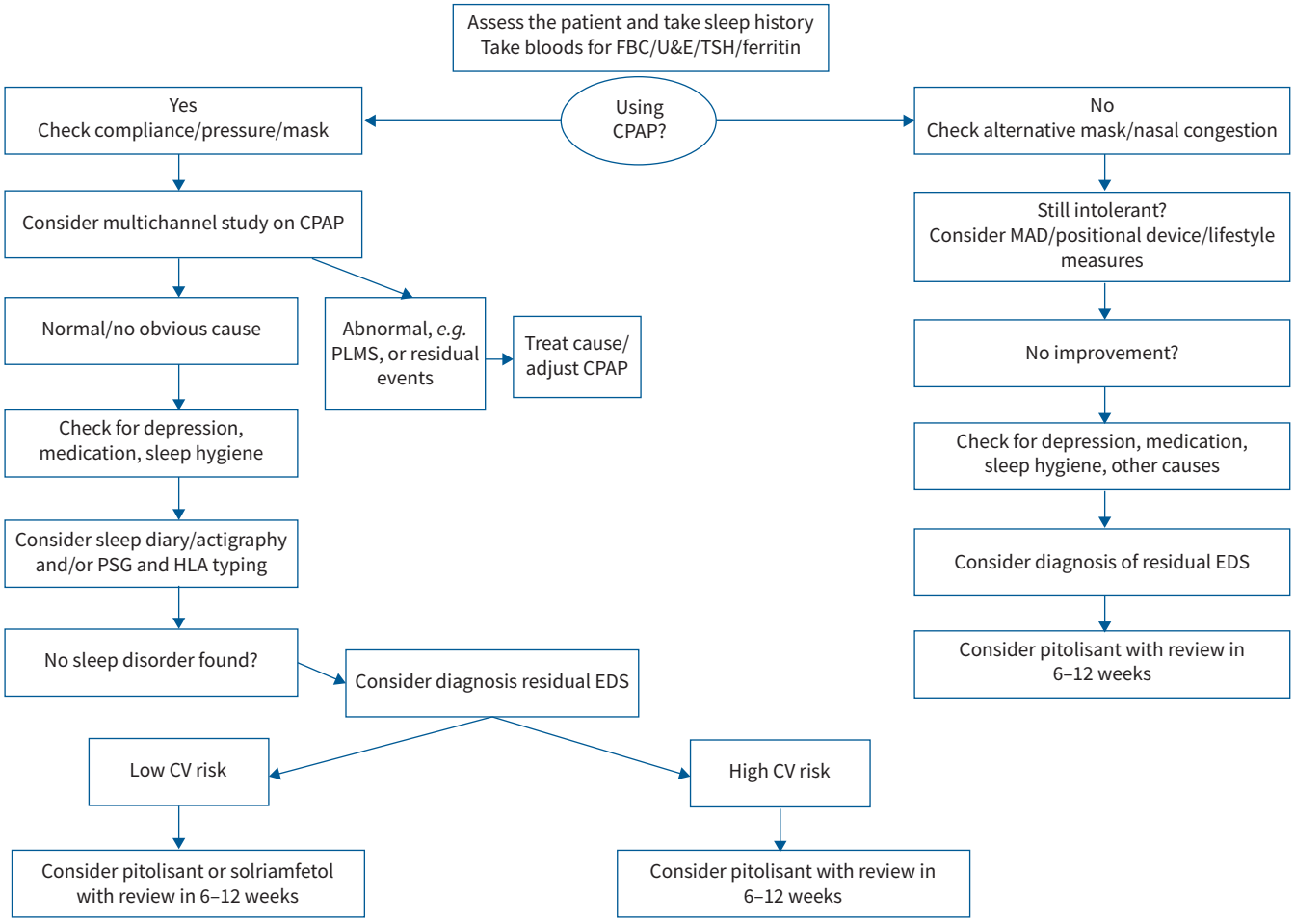

FIGURE 1 How to manage excess daytime sleepiness (EDS) in a specialist sleep clinic. CPAP: continuous positive airway pressure; CV: cardiovascular; FBC: full blood count; HLA: human leukocyte antigen; MAD: mandibular advancement device; PLMS: periodic limb movements of sleep; PSG: polysomnography; TSH: thyroid-stimulating hormone; U&E: urea and electrolytes.

suspicion and additional diagnostic tests during positive airway pressure (PAP) treatment have been recommended in patients with persistently elevated AHI on treatment [39, 40] since the reliability of event identification by the PAP device algorithm may be far from optimal [41, 42]. PAP treatment may also be associated with treatment-emergent central sleep apnoea, especially in the first period of use [43], which resolves spontaneously over time in most cases [44]. Finally, poor adherence to PAP treatment, *i.e.* average nightly use for less than 4 $h \cdot night^{-1}$ over at least 70% of the nights, can be responsible for persistence of OSA symptoms including EDS.

When CPAP-related factors are ruled out, other possible causes of persistent EDS should be assessed. The most common cause of EDS in the general population is insufficient sleep duration, which should always be excluded, possibly by objective measurements such as actigraphy. The age of the patient, particularly for those over 75, should be taken into account and has been linked to daytime sleepiness [45] probably reflecting the increasing burden of comorbidities. A further expansion of the effect of this demographic is described in a recent review by Zinchuk and Yaggi [46], which showed that not only do older patients become more sleepy, but the older patients with most comorbidities obtain the least improvement with CPAP therapy.

Depression is another common cause of EDS, either directly or through the effects of psychotropic drugs, and is often associated with OSA [47]. Comorbid sleep disorders, such as the occurrence of restless leg syndrome, periodic leg movements (PLMs), or more rarely narcolepsy or idiopathic hypersomnia, or neurologic diseases associated with EDS, should also be investigated, especially when RES is severe

despite optimal treatment for OSA. A full history of ongoing medical treatment may uncover the use of drugs causing sleepiness, *i.e.* hypnotics. Finally, medical conditions such as metabolic disorders (diabetes, obesity, hypothyroidism, among others) can be associated with EDS independent of OSA, through a state of low-grade inflammation. It is known that obesity is a potential cause of EDS, even in the absence of OSA [48, 49]. The role of obesity in the pathogenesis of EDS is supported by its improvement/resolution after weight loss [50], independent of changes in AHI [51].

Table 2 summarises the available studies on RES in CPAP-treated OSA patients. A study assessing EDS in treated OSA patients and in subjects from the general population reported a similar prevalence of EDS in both groups (with a bell-shaped curve of ESS), but the potential causes of EDS were not investigated and the groups were not well matched for sex or body mass index [52]. One multicentre randomised controlled trial assessed EDS monthly for the first 3 months of CPAP use, and showed a progressive decrease in its prevalence from 60% to 17%, together with significant sleep disruption during CPAP treatment documented by actigraphy [53]. The majority of studies were observational, either multicentre [5, 54–57] or single-centre [47, 53, 58–60]. These studies reported a variable prevalence of EDS in treated OSA patients, and follow-up duration varied from 3 to 24 months. All studies took into account the average nightly use of CPAP, since a clear relationship has been shown between adherence to treatment and decrease in ESS [5]. Similarly, the possibility of incomplete resolution of OSA was ruled out as a cause of RES, and a study underlined the high sensitivity of methods based on pulse arterial tonometry compared to traditional polygraphy in patients with residual EDS [61]. On average, prevalence of EDS was high in the first months of treatment, and declined thereafter. Results in patients using mandibular advancement devices were similar to those in patients using CPAP [60]. Studies agree that a high ESS at baseline increases the risk of remaining sleepy on CPAP treatment [47, 54, 57, 60, 62]. As for the impact of OSA severity assessed as AHI, mild-moderate rather than severe OSA was more often associated with RES [47, 56, 57]. One study investigated the possible role of PLMs in patients with RES, and reported a quite high prevalence of PLMs (38.5%) but no association with EDS [58]. Some studies investigated the role of depression [47, 54, 63], which is a major determinant of sleepiness in the general population. In addition, in most cases evaluation of EDS was based on subjective reports, rather than on objectively documented sleepiness. Vernet *et al.* [63] extensively studied 20 patients with RES and good adherence to CPAP after at least 6 months of treatment but RES in well-treated OSA patients was hard to explain. Moreover, the criteria defining central hypersomnia occurred only in 15% of the patients, and EDS responded poorly to wake-promoting drugs like modafinil. The accompanying editorial highlighted the lack of clinical descriptors of RES and suggested it might reflect an individually altered sensation, similar to what happens in subjects with a heightened perception of pain [3].

Some studies used both subjective and objective tests for EDS. In the study by Budhiraja *et al.* [62], there was a good agreement between the prevalence of ESS >10 and of sleep latency at MWT <17 min (22.3% *versus* 23%). A recent study in 29 patients with RES (average ESS 16.3±2.3) and good adherence to CPAP (about 7 h·night^{-1}) reported that 66% of the patients showed moderate-severe EDS assessed as sleep onset between <8–11 min, but no relationship was found between sleep latency and ESS [64].

Finally, in a small group of patients with EDS on CPAP, a fluorodeoxyglucose-positron emission tomography study found reduced glucose utilization in the frontal area, but lacked a control group [65]. Conversely, other studies have shown that RES on CPAP treatment was associated with changes in cerebral magnetic resonance imaging especially regarding white matter, which correlated with the post-CPAP changes in psychomotor vigilance test and ESS [66, 67]. Improvement in cerebral imaging technology is expected to provide more data and allow a deeper understanding of the dysfunction associated with persistent EDS in treated OSA.

Future studies on residual EDS in OSA patients should also take into account the spontaneous variability of EDS documented in the general population. In a longitudinal study from Canada, based on data obtained by an annual online survey, 33% of the subjects were sleepy at baseline; over follow-up, initially sleepy subjects showed persistent EDS in 33%, intermittent EDS in 44%, and remitted EDS in 23% of cases [68]. The authors analysed predictors of improved EDS, which included a healthy lifestyle, normal body weight, low use of hypnotics, sufficient nightly sleep, and lack of insomnia or depressive symptoms. These results further highlight the complexity of the EDS symptom, and possible areas susceptible to educational interventions.

In addition to clinical studies, we should also consider the underlying pathological effects of RES and whether treating it could prevent cognitive decline. It has been hypothesised that OSA may cause irreversible hypoxic brain damage, thus accounting for the persistence of EDS after initiation of CPAP

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TABLE 2 Summary of studies on residual sleepiness (RES) after obstructive sleep apnoea (OSA) treatment

First author, year [ref.]	Study type	Sample	Tests used	Results	Comments
Patel, 2003 [74]	Meta-analysis	11 RCTs: subjective sleepiness (ESS) Eight RCTs: objective sleepiness (MSLT, MWT)	CPAP treatment for 4–24 months	Greater decrease in ESS after CPAP in studies recruiting patients with severe OSA and EDS Sleep onset latency increased after CPAP by 1 min compared to placebo	RES mentioned in the discussion but not analysed
Haba-Rubio, 2005 [58]	Observational study in OSA patients	57 consecutive patients studied at baseline and after CPAP treatment	ESS, PLMS; 1 year of CPAP treatment	Prevalence of PLMS at follow-up: 38.5% PLMS not correlated with RES	
Weaver, 2007 [5]	Multicentre observational study in OSA patients	149 patients with severe OSA studied at baseline and after CPAP treatment	ESS (n=106), MSLT (n=85); FOSQ (n=120); 3 months	Prevalence of RES (ESS score >10): 77.4% at baseline and 34% post-CPAP Prevalence of RES decreased with increasing CPAP use About 20% of patients using CPAP for >8 h remained sleepy at follow-up	Important paper reporting data on both subjective and objective sleepiness before/after treatment; MSLT results were in line with those obtained by ESS
Stradling, 2007 [52]	OSA *versus* community subjects	525 controls *versus* 572 patients on CPAP	ESS, home sleep study, single time point	ESS >10 in 14.3% controls *versus* 16.1% in post-CPAP group p=0.54	Non-matched controls, many sleepy subjects in the general population, causes of EDS not investigated
Antczak, 2007 [65]	PET study in OSA patients with persistent EDS post-CPAP treatment	Small observational study (seven out of 13 patients with RES)	FDG-PET scan; at least 12 months off CPAP treatment	Prevalence of RES (ESS >12): 7.8% (13/167 patients) Vigilance test abnormal in five out of seven patients studied Reduced glucose utilisation in the frontal area was the most common PET abnormality	Small number of patients studied, no control group
Pépin, 2009 [54]	Multicentre observational study in OSA patients	502 compliant CPAP users	ESS, QoL (NHP); 1 year	ESS ⩾11 in 12% but 6% after exclusion of PLMS, depression, narcolepsy	Patients with residual EDS were younger and sleepier at time of OSA diagnosis
Koutsourelakis, 2008 [47]	Single-centre observational study in OSA patients	208 compliant CPAP users	ESS; 6 months	Depression in 38.8% of patients with RES	Other predictors: diabetes, heart disease, higher ESS and lower RDI at baseline
Antic, 2011 [55]	Multicentre clinical effectiveness cohort study	174 moderate to severe OSA on CPAP	ESS, MWT, SF36, FOSQ, neurocognitive function; 3 months	RES in 40%, MWT normal in 70%, vitality improved with adherence Vigilance (average reaction time) did not improve with CPAP	% patients achieving normal ESS and FOSQ was correlated with hours of usage MWT did not improve with increased CPAP usage
Vernet, 2011 [63]	Single-centre observational case-control study in OSA patients	20 OSA patients with RES on CPAP with good adherence, 20 age- and sex-matched OSA patients without RES, 20 healthy controls	ESS, several questionnaires including fatigue severity score, BDI, HAD score, PSG, MSLT, cognitive tests; CPAP for at least 6 months	RES associated with lower amount of nREM 3 sleep, higher PLM rate, and HAD and fatigue scores Central hypersomnia criteria in 15% of RES group, clinical profile of EDS different from narcoleptic patients (including poor response to modafinil)	Exclusion criteria: abnormal sleep duration, use of sedative drugs or alcohol, night shift work, narcolepsy, severe RLS, neurological or psychiatric disease

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TABLE 2 Continued

First author, year [ref.]	Study type	Sample	Tests used	Results	Comments
Gasa, 2013 [56]	French National Sleep Registry	OSA patients treated with CPAP, exclusion of those using CPAP <3 h·night^{-1}, with residual AHI ⩾15 events·h^{-1} or major depression (n=1047)	RES: ESS ⩾11; follow-up: 3–24 months	Prevalence of RES: 13% in the whole group (18% in patients with EDS at baseline); decreased with increasing CPAP use Higher prevalence of heart failure in the RES group; RES more frequent in moderate than in severe OSA	No sleep study at follow-up
Lau, 2013 [59]	Single-centre observational study in OSA patients	Moderate to severe OSA patients on CPAP with good adherence (n=37) and healthy controls (n=27)	ESS, PSQI, BDI, POMS, FOSQ; ⩾3 months (mean follow-up duration 18±11 months)	RES in 30% of the OSA sample *versus* 15% of controls (NS) Psychosocial and functional outcomes associated with EDS level and sleep quality post treatment	RES-predicted psychosocial outcomes Predictors of RES not investigated
Verbruggen, 2014 [60]	Single-centre observational study in OSA patients	185 OSA patients treated with MAD, 84 with complete response (45% with AHI >5 events·h^{-1})	PSG, ESS; 3 months	RES in 32% of patients with normalised AHI on MAD Less nREM 3 sleep in patients with RES Predictors of RES in this group: high baseline ESS score, younger age	
Tippin, 2016 [53]	Single-centre observational study in OSA patients	Newly diagnosed OSA patients (n=80) and age- and education-matched controls from the general population (n=50)	Actigraphy, PSG, ESS, FOSQ, monthly visits for 3 months after start of CPAP	Prevalence of ESS score >10 decreased from 60% to 17% after CPAP for 3 months Actigraphic evidence of persistent sleep disruption on CPAP (high WASO, low sleep efficiency) and gradual improvement of ESS and FOSQ over time	Incomplete normalisation of sleep on CPAP
Budhiraja, 2017 [62]	Prospective multicentre RCT (Apnoea Positive Pressure Long-term Efficacy Study)	558 OSA patients randomised to active CPAP	PSG, MWT (n=380), ESS Follow-up: 6 months	ESS score >10 in 22.3% of the sample at 6 months (18.1% in good CPAP users) Sleep latency at MWT <17 min in 23%	Use of CPAP and ESS at baseline were the only significant predictors of EDS at 6 months
Xiong, 2017 [66]	Single-centre observational study in OSA patients	29 male severe OSA patients aged 30–55 years, treated with CPAP for ⩾6 h·night^{-1}	Sleepiness assessed by ESS and PVT; actigraphy, MRI scan; CPAP treatment for at least 30 days	RES prevalence: 41% (12/29) RES was associated with white matter changes, indicated by changes in median and radial diffusivity in whole brain and specific regions These changes correlated with PVT and ESS changes post CPAP	
Schöbel, 2018 [61]	Prospective randomised crossover study	49 consecutive OSA patients (39 male) on CPAP treatment	Six-channel PG *versus* WatchPat ESS, CPAP adherence Follow-up: 81±63 months	RES in 12 patients (24.5% of the sample) Higher sensitivity of WatchPAT *versus* PG in detecting respiratory events (positive predictive value 41.7% *versus* 16.7%)	Study centred on screening methods for RES WatchPAT more sensitive to autonomic events than PG

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TABLE 2 Continued

First author, year [ref.]	Study type	Sample	Tests used	Results	Comments
Zhang, 2019 [67]	Single-centre observational study in OSA patients	27 male severe OSA patients aged 30–55 years, treated with CPAP for ⩾6 h·night^{-1}	Sleepiness assessed by ESS and PVT; actigraphy, diffusion MRI scan; CPAP treatment for at least 30 days	RES prevalence: 33% (9/27); in the whole brain, temporal diffusion heterogeneity α and anomalous diffusion coefficient D_m in sleepy *versus* non-sleepy patients; differences in temporal and diffusion heterogeneity (α and β) and D_m in 12 fibre tracts between sleepy and non-sleepy patients	Extends previous results by Xiong *et al.* [66]
Foster, 2020 [64]	Retrospective clinical study	29 OSA patients (23 male) with good adherence to CPAP and RES (ESS >10)	ESS, PSG, MSLT, actigraphy	AHI on CPAP <10 events·h^{-1} CPAP use: 7.0±0.9 h·night^{-1} Average ESS score: 16.3±2.3 SOL: <8 min in 31% (severe EDS), 8–11 min in 35% (moderate EDS), >11 min in 35% of the patients (no EDS) Short sleep excluded by actigraphy	Relatively young subjects (mean age±SD: 41±11 years) No difference in ESS between SOL groups
Bonsignore, 2021 [57]	Retrospective multicentre study (ESADA Cohort)	4853 OSA patients on CPAP at first follow-up visit; 2190 of them with sleep monitoring data	ESS, PSG or PG; median follow-up 5 months (IQR 3–13 months)	ESS >10 in 56% of patients at baseline, and in 28.2% of patients at follow-up (n=4853) ESS >10 on CPAP treatment was associated directly with ESS score at baseline, and inversely with duration of follow-up, and CPAP use (R^2 of the model: 0.417)	Highest prevalence of EDS (40%) in the first 3 months of treatment

AHI: apnoea/hyponoea index; BDI: Beck Depression Inventory; CPAP: continuous positive airway pressure; EDS: excessive daytime sleepiness; ESS: Epworth Sleepiness Scale; FDG: fluorodeoxyglucose; FOSQ: functional outcomes of sleep questionnaire; HAD: hospital anxiety and depression; IQR: interquartile range; MAD: mandibular advancement device; MRI: magnetic resonance imaging; MSLT: multiple sleep latency test; MWT: maintenance of wakefulness test; NHP: Nottingham Health Profile; nREM: non-rapid eye movement; NS: not statistically significant; PET: positron emission tomography; PG: polygraphy; PLM: periodic leg movement; PLMS: periodic leg movements during sleep; POMS: profile of mood states; PSG: polysomnogram; PSQI: Pittsburgh Sleep Quality Index; PVT: psychomotor vigilance task; QoL: quality of life; RCT: randomised controlled trial; RDI: respiratory disturbance index; RLS: restless legs syndrome; SF36: short form 36; SOL: sleep onset latency; WASO: wakefulness after sleep onset.

treatment. This hypothesis has been tested in animal models of chronic intermittent hypoxia or sleep fragmentation, but data in humans are scarce, since the majority of human studies aimed at assessing cognitive impairment without a specific focus on RES. Assessment of sleepiness in mice required the development of a protocol to perform MSLT, by taking into account the wake–sleep pattern typical of murine species [69].

Chronic intermittent hypoxia exposure for 6 months was associated with loss of 40% of wake-promoting catecholaminergic neurons in rodents [70], possibly explained by white matter loss [71] and vicious cycles of oxidative stress causing damage involving both neurons and microglia [72]. Similarly, neuronal damage in wake-active regions was found after 4 weeks of sleep fragmentation [73]. These studies are important pieces of evidence, but due to the lack of data in humans, the role of hypoxic damage in the pathogenesis or residual EDS remains currently unproven.

History of treatments for EDS in addition to CPAP

The concept of RES and recognition of the need to develop pharmacotherapy for treating RES in CPAP-treated patients appeared during the late 1990s. There was initially an intense debate regarding RES as a true pathological entity as some leading experts assumed that the prevalence of EDS in CPAP-treated OSA simply reflected a prevalent complaint in the general population [75].

The first pivotal studies evaluating modafinil and armodafinil as adjunct therapy in CPAP-treated patients were conducted in the years 2000–2010 [76, 77]. Modafinil, which had been used in narcolepsy since the early 1990s [78], was then used internationally to treat RES in OSA and was reported as improving the ESS score by ∼2 points and the MWT by ∼3 min over placebo [79, 80].

In addition, there was interest in modafinil as a possible adjunct during CPAP holidays to maintain neurobehavioural functioning (see table 3). This was explored by Williams *et al.* [81] in a small crossover study where the subjects used CPAP for four nights with one night off and then received either modafinil or placebo. Driving simulation, sleep diaries, cortical activation measures and subjective sleep questionnaires were used to investigate whether modafinil could prevent decline in function. Although a small study, it did show subjective but not objective maintenance of function, which the authors were concerned about in case this gave false reassurance to the user. However, this was a short withdrawal where CPAP may have masked the real decline that would be seen during longer withdrawal periods.

The next study [82], also by the Sydney group, looked at a longer withdrawal period of two nights again in a crossover design. During the withdrawal, severe sleep-disordered breathing was seen and, in this case, modafinil did improve simulated driving performance as well as subjective sleepiness. The authors concluded that modafinil could be used to ameliorate performance when CPAP therapy was disrupted for some reason such as travelling or infections.

TABLE 3 Effect of modafinil on continuous positive airway pressure (CPAP) withdrawal

First author, year [ref.]	Methods and setting	Participants	Intervention	Outcomes	Results
Williams, 2008 [81]	RCT, crossover Sydney	n=12, ESS 6.4±3.1, CPAP users	CPAP withdrawal one night then modafinil *versus* placebo	Driving simulation, STISIM, CFF, PSQI, FSS, CPAP diary, ESS, SSS	No change in reaction times, CFF Sleepiness reduced with modafinil (SSS p=0.03)
Williams, 2010 [82]	RCT, double-blind placebo-controlled crossover Sydney	n=21, male, CPAP users	CPAP withdrawal 2 nights then modafinil *versus* placebo	Driving simulation, PVT, KSS	Modafinil improved PVT, driving simulation, KSS (p=0.01)
Wang, 2015 [83]	RCT, double-blind placebo-controlled crossover Sydney	n=23, male CPAP users	CPAP withdrawal 2 nights then modafinil *versus* placebo	Driving simulation, PVT, KSS, PSG, awake EEG	Modafinil improved EEG activation which correlates to improved neurocognitive performance and reduced sleepiness

CFF: critical flicker fusion; EEG: electroencephalography; ESS: Epworth Sleepiness Scale; FSS: fatigue severity scale; KSS: Karolinska Sleepiness Scale; PSG: polysomnogram; PSQI: Pittsburgh Sleep Quality Index; PVT: psychomotor vigilance task; STISIM: driving simulator; RCT: randomised controlled trial; SSS: Stanford Sleepiness Scale.

WANG *et al.* [83] further showed that CPAP withdrawal (with the same protocol) led to general slowing of electroencephalography (EEG) and this improved with modafinil. Alpha/delta ratio was a key biomarker of EEG activation, showing a correlation with improved subjective sleepiness and driving simulator performance with modafinil. This removes the subjective nature of some of the previous work as there is a clearer neurobiological pathway from EEG to sleepiness and performance.

In addition, a study from the Sydney group [84] showed that CPAP naïve subjects with mild to moderate OSA (AHI=5–30 events·h^{-1}) with ESS 13.6 (3.3) also showed improvement in ESS and driving performance in a similar way to the withdrawal studies. The effect size on ESS with modafinil was greater than with CPAP in this group possibly due to poor levels of adherence in these patients. It should be noted that despite these studies modafinil is only licensed for narcolepsy in Australia.

During the same period, robust evidence was published regarding epidemiology, prevalence and clinical phenotypes of RES in OSA [54, 56], suggesting that this was a real syndrome that could benefit from treatment. However, there were safety concerns regarding modafinil/armodafinil and in 2011 the European Medicines Agency withdrew this indication owing to a poor benefit/risk ratio. It was considered that the risk of serious cardiovascular, neuropsychiatric, skin and hypersensitivity disorders prevailed over any potential benefit of treating residual EDS in patients with OSA. Thus, from 2011 to 2020 no pharmacological treatment was available in Europe for RES or as an adjunct to CPAP in OSA and only modafinil off-label use continued in a limited number of patients. Currently, modafinil and armodafinil remain approved in the United States, but not in Europe.

From 2019 to 2021, the efficacy of solriamfetol, a dopamine/norepinephrine reuptake inhibitor, has been established in randomised controlled trials and long-term open label studies (table 4).

The initial study, TONES 3, [85], in 476 adults with OSA who were currently treated with CPAP, mandibular advancement device or surgery showed a dose-dependent improvement in subjective sleepiness (ESS decreased by 2–5 points) and objective sleepiness (MWT improved by 5–13 mins) compared with placebo over a 12-week period. There was also a dose-dependent response in cardiovascular effects with 300 mg giving a small rise in blood pressure. In a randomised withdrawal study, TONES 4, it was demonstrated that improvements in sleepiness were maintained in the active group compared to those withdrawn from the medication. It also showed no rebound phenomena once the drug was withdrawn [86]. A longer-term study in patients with narcolepsy or OSA, TONES 5 [87], showed that the short-term effects shown in these initial studies are maintained in both type of patients over a 6-month period. Solriamfetol has been approved in the United States and EU in 2020 at the 150 mg dosage for OSA, which shows small effects on blood pressure.

Pitolisant, a selective histamine receptor 3 antagonist/inverse agonist, has been used worldwide to treat EDS and cataplexy in narcolepsy very effectively for a number of years following the HARMONY 1 randomised placebo-controlled trial [88]. More recently, two pivotal studies have demonstrated efficacy of pitolisant in two distinct populations of OSA patients, adherent to CPAP [89] and refusing or not tolerating CPAP [90], respectively. In HAROSA 1 (n=244), CPAP-adherent patients showed an improvement in ESS and the Oxford Sleep Resistance Test (a behavioural MWT test) with no safety concerns. HAROSA 2 investigated 268 adults with OSA who had refused CPAP and showed a 2.8-point improvement in ESS with no cardiovascular or safety concerns. There will be long-term data for pitolisant in the OSA population published soon, but in the meantime pitolisant has been approved, at the 20 mg dose, in the EU in 2021 for these two distinct indications.

There will be concerns from sleep physicians that clinical trials involving patients who are intolerant of CPAP have been carried out and could lead to higher rates of non-use if stimulants were prescribed. However, consistent data from large-scale studies are demonstrating that the rate of CPAP termination is up to 45% at 3 years after CPAP initiation [91]. Implementation of alternatives to CPAP remain limited in routine practice [15, 92], and the majority of these patients stay untreated. Recent data demonstrate in real-life that CPAP discontinuation is associated with an increase of 39% in mortality rates [93]. Beyond mortality, quality of life and fitness to drive are altered in a subgroup of these patients. For these reasons, research was conducted to address efficacy of stimulants in this specific situation of untreated or nonadherent OSA [94, 95]. In these studies, the range of efficacy for improving sleepiness was the same for adherent and nonadherent patients. Other drugs such as methylphenidate, used in narcolepsy, are unlikely to be used in this patient group due to their high cardiovascular risk profile, which also makes it difficult to design clinical trials using these medications. There is a dilemma for sleep physicians with all these wake-promoting agents as there is potential harm against the benefits of improving symptoms of RES. Therefore, for these reasons, prescription, if any, in patients without primary therapy for OSA

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TABLE 4 Summary of clinical studies investigating novel wake-promoting drugs in obstructive sleep apnoea (OSA) (solriamfetol and pitolisant)

First author, year [ref.]	Study type	Sample	Tests used	Results	Comments
Schweitzer, 2019 [85]	OSA TONES 3 Phase 3 randomised double-blind placebo-controlled; 12 weeks solriamfetol once daily (37.5 mg/75 mg/150 mg/300 mg *versus* placebo)	476 adults with OSA current or prior use of CPAP, MAD or surgery ESS ⩾10, sleep latency on MWT <30 mins, usual night sleep ⩾6hrs Randomisation stratified by adherence (>4 h) or non-adherence (<4 h)	Co-primary endpoints: change from baseline to 12 weeks in MWT and ESS Secondary endpoints: PGI-C and CGI-C	MWT: change from baseline compared with placebo (95% CI): 37.5 mg 4.5 (1.2–7.9) p=0.0086, 75 mg 8.9 (5.6–12.1) p<0.0001, 150 mg 10.97 (8.1–13.4), p<0.0001, 300 mg, 12.8 (10.0–15.6), p<0.0001 ESS: change from baseline compared with placebo (95% CI): 3.75 mg −1.9 (−3.4–−0.3), p=0.0161, 75 mg −1.7 (−3.2–−0.2) p=0.0233, 150 mg −4.5 (−5.7–−3.2), p<0.0001, 300 mg −4.7 (−5.9–−3.4), p<0.0001	Good dose-dependent response in wakefulness as defined by MWT increase and reduction in ESS Best response with highest dose (300 mg) Dose response in cardiovascular physiological effects such as BP and heart rate with 300 mg showing small but statistically significant rise in BP (2.5 (0.4–4.6))
Strollo, 2019 [86]	OSA TONES 4 Phase 3 enriched randomised withdrawal study 2 weeks of solriamfetol dose 75, 150 or 300 mg *versus* placebo in withdrawal phase	124 adults were randomised to withdrawal or continue on active drug following a screening (only those with improvement entered), titration and stable dose phase	Co-primary endpoints: change from baseline to 12 weeks in MWT and ESS Secondary endpoints: PGI-C and CGI-C	MWT during withdrawal phase difference from placebo mean (95% CI): 11.2 (7.8–14.6), p<0.0001 ESS during withdrawal phase difference from placebo mean (95% CI) −4.6 (−6.4–−2.8), p<0.0001	Improvements in sleepiness were maintained compared to the group who were randomised to placebo (withdrawn) No rebound hypersomnia or withdrawal adverse events Enriched population including only those who had a positive response to the drug during the stable phase May not be the same level of response in the general population
Malhotra, 2020 [87]	TONES 5 Long-term study (narcolepsy or OSA) 2 weeks of titration followed by maintenance phase At 6 months subgroups were randomised to solriamfetol or placebo and underwent 2-week withdrawal	417 patients with OSA, 226 patients with narcolepsy in long-term follow-up phase 282 entered randomised withdrawal phase	Primary endpoint: change in ESS Secondary endpoint: change in PGI-C and CGI-C	Mean difference from placebo during withdrawal phase: −3.7 (−4.8–−2.65), p<0.0001	Showed that the response is maintained longer term The effect was consistent across the narcolepsy and OSA groups

Continued

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TABLE 4 Continued

First author, year [ref.]	Study type	Sample	Tests used	Results	Comments
Pépin, 2021 [89]	HAROSA 1 Phase 3 double-blind randomised placebo-controlled study 12 weeks of pitolisant at 3:1 *versus* placebo	244 adult patients with OSA who were compliant with CPAP therapy	Primary endpoint: change in ESS Secondary endpoints: included OSLER test and EQ-5D as well as safety data	Mean difference from placebo (95% CI): –2.6 (–3.9—1.4), p<0.001	Significant reduction in subjective and objective sleepiness when used as an adjunct to CPAP therapy There were no safety concerns with good improvements in patient- and physician-reported health outcomes
Dauvilliers, 2020 [90]	HAROSA 2 Phase 3 double-blind randomised placebo-controlled study 12 weeks of pitolisant at 5/10/20 mg (3:1) *versus* placebo	268 adult patients with OSA who were unable to use CPAP therapy	Primary endpoint: change in ESS Secondary endpoints: included OSLER test and EQ-5D as well as safety data	Mean difference from placebo (95% CI): −2.8 (−4.0–−1.5), p<0.001	Significant response in ESS in this group and safety data showing that there were no significant adverse events in non-CPAP users

BP: blood pressure; CGI-C: clinical global impression of change; CPAP: continuous positive airway pressure; EQ-5D: European Quality of Life–five dimensions; ESS: Epworth Sleepiness Scale; MAD: mandibular advancement device; MWT; maintenance of wakefulness test; OSLER: Oxford Sleep Resistance; PGI-C: patient global impression of change.

probably requires it to be strictly limited to expert centres after appropriate evaluation and a cautious follow-up regarding safety.

Future research questions

- Should the indications of wake-stimulating agents be limited to OSA patients adequately treated by CPAP or extended to those not tolerating primary therapy?
- Prospective registries should be implemented to assess long-term benefits and safety, specifically in OSA with cardiometabolic comorbidities including cognitive deficits.
- What is the impact of stimulants on CPAP adherence with attention specially paid to the subgroup of intermittent users?
- Could wake-promoting agents favour a healthier lifestyle, *e.g.* increased physical activity?
- Would resolution of EDS help improve cognition?
- What parameters would a sleep physician use to decide on a particular wake-promoting agent?

Conclusions

EDS is a major but not universal feature of OSA. The majority of population-based data imply that EDS is a marker of poor outcome, but the prognostic role of persistent EDS in treated patients is unknown although animal models appear to suggest a link with cognitive decline.

In the meantime, sleep physicians now have more varied treatments available for OSA and RES. These newer drugs potentially allow us to treat CPAP adherent and nonadherent patients without the cardiovascular concerns associated with older medications. However, available data suggest that assessment of RES should only be considered after the first 6 months of treatment, since EDS may spontaneously resolve in about half of sleepy patients [57].

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