Respir. Med and Res 86 (2024) 101105

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Recommendations

Guidelines for the assessment and management of residual sleepiness in obstructive apnea-hypopnea syndrome
Endorsed by the French Sleep Research and Medicine Society (SFRMS) and the French Speaking Society of Respiratory Diseases (SPLF)

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Abbreviations: AASM, American Academy of Sleep Medicine; MA, Market Authorization; BDI, Beck Depression Inventory; CGI-C, Clinical Global Impression of Change; CV, Cardiovascular; ESS, Epworth Sleepiness Scale; EEG, Electroencephalogram; EQ-5D, European Quality of Life scale - five dimensions; HR, Heart rate; FDG, Fluorodeoxyglucose; FOSQ, Functional Outcomes of Sleep Questionnaire; HAD, Hospital Anxiety and Depression Scale; HAS, National Health Authority (France); PAH, Pulmonary arterial hypertension; AHI, Apnea/hypopnea index; IHSS, Idiopathic Hypersomnia Severity Scale; MRI, Magnetic resonance imaging; IRSNa, Serotonin and noradrenaline reuptake inhibitors; ISRS, Selective serotonin reuptake inhibitors; PR, Prolonged release; ABPM, Ambulatory blood pressure monitoring; NHP, Nottingham Health Profile; MAD, Mandibular advancement device; BP, Blood pressure; PGI-C, Patient Global Impression of Change; PHQ4, Patient Health Questionnaire; PLMS, Periodic legs movements during sleep; PNDS, National Diagnosis and Care Protocol (France); POMS, Profile of mood states; PPC, Continuous positive airway pressure; PSG, Polysomnography; PSQI, Pittsburgh Sleep Quality Index; RP, Respiratory polygraphy; PVT, Psychomotor vigilance task; RERA, Respiratory effort related arousal; RDI, Respiratory Disturbance Index; SAS, Sleep apnea syndrome; OSAHS, Obstructive sleep apnea-hypopnea syndrome; EDS, Excessive daytime sleepiness; rEDS, residual excessive daytime sleepiness; SF36, Short Form 36; SFRMS, Sleep Research and Medicine French Society (Société Française de Recherche et Médecine du Sommeil); SPLF, French Speaking Society of Respiratory Diseases (Société de Pneumologie de Langue Française); PET, Positron emission tomography; MSLT, Multiple Sleep Latency Test; MWT, Maintenance of Wakefulness Test; PPV, Positive predictive value

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https://doi.org/10.1016/j.resmer.2024.101105

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ARTICLE INFO

Article History:
Received 15 March 2024
Accepted 18 March 2024
Available online 6 April 2024

→ Publication en français dans la revue Médecine du Sommeil en aout 2023 : https://doi.org/10.1016/j.msom.2023.06.001

Keywords:
Residual sleepiness
sleep apnea
Consensus
Recommendations
Stimulant

ABSTRACT

Excessive daytime sleepiness (EDS) is frequent among patients with obstructive sleep apnea hypopnea syndrome (OSAHS) and can persist despite the optimal correction of respiratory events (apnea, hypopnea and respiratory efforts), using continuous positive airway pressure (CPAP) or mandibular advancement device. Symptoms like apathy and fatigue may be mistaken for EDS. In addition, EDS has multi-factorial origin, which makes its evaluation complex. The marketing authorization [*Autorisation de Mise sur le Marché* (AMM)] for two wake-promoting agents (solriamfetol and pitolisant) raises several practical issues for clinicians. This consensus paper presents recommendations of good clinical practice to identify and evaluate EDS in this context, and to manage and follow-up the patients. It was conducted under the mandate of the French Societies for sleep medicine and for pneumology [*Société Française de Recherche et de Médecine du Sommeil* (SFRMS) and *Société de Pneumologie de Langue Française* (SPLF)]. A management algorithm is suggested, as well as a list of conditions during which the patient should be referred to a sleep center or a sleep specialist. The benefit/risk balance of a wake-promoting drug in residual EDS in OSAHS patients must be regularly reevaluated, especially in elderly patients with increased cardiovascular and psychiatric disorders risks. This consensus is based on the scientific knowledge at the time of the publication and may be revised according to their evolution.

1. Introduction

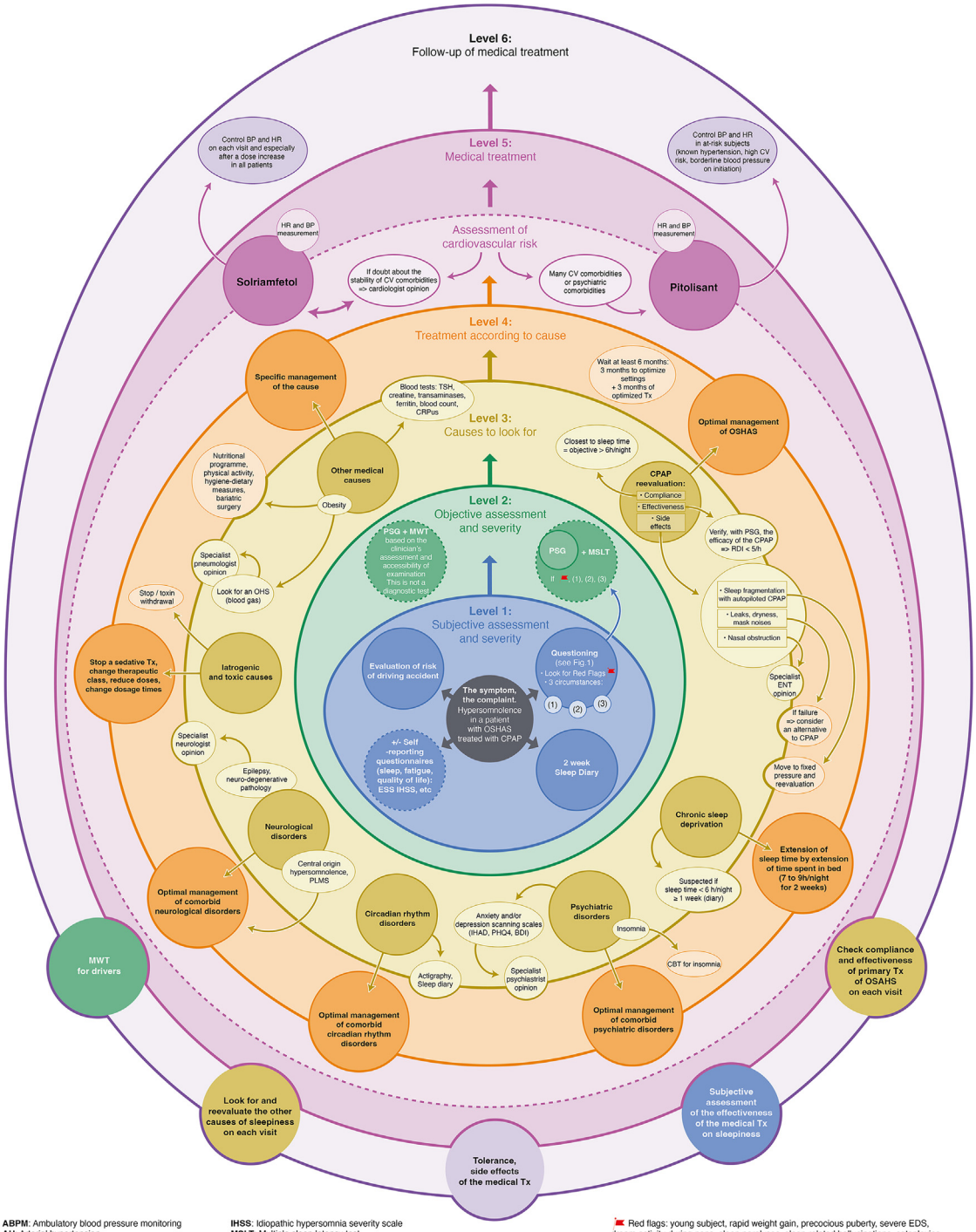
Complete (obstructive apnea) or partial (obstructive hypopnea) closure of the upper airways for at least 10 s resulting from reduced pharyngeal muscle tone is a frequent phenomenon during sleep causing a brief awakening and/or drop in oxygen saturation. These events, if repetitive, induce intermittent hypoxia and impact cardiovascular health. The number of apneas and hypopneas per hour of sleep is known as the apnea-hypopnea index (AHI). One in 4 women and one in 2 men over the age of 40 present with an AHI > 15/h [1]. This higher AHI score can be associated with hypersomnolence (in one of every 5 cases) and an increased risk of arterial hypertension, stroke, depression and mortality in the general population [2]. That said, since there is a lack of evidence supporting the benefits of wide scale screening and treatment [3] systematic screening of asymptomatic patients for nocturnal breathing disorders is not recommended.

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is defined as the association of an AHI>5/h with nocturnal (polyuria, suffocation, loud snoring, hyper-sudation) and daytime symptoms (excessive daytime sleepiness (EDS), morning fatigue, irritability, low mood, erectile dysfunction, attentional disorders) for which there is no better explanation than respiratory events during sleep. OSAHS is common; its prevalence increases with age, obesity and male sex [4]. EDS is one of the cardinal symptoms of the diagnosis. It is associated with a change in quality of life, lower attention and a higher risk of road accidents. It is often improved by correcting nocturnal apneas and hypopneas with continuous airway pressure (CPAP) or a mandibular advancement device (MAD), which suggests a causal link between AHI and EDS. But EDS can persist in 10 to 55 % of patients (20 % on average, see Table S1) despite optimal primary treatment of the apnea: determining if the sleepiness has other causes such as (often associated) obesity, depression, or sleep deprivation (in which case high AHI is an incidental association) or if it results from central damage to the arousal systems exposed for years to intermittent nocturnal hypoxia is a complex process. The high prevalence and frequency of residual EDS (rEDS) after apneas and hypopneas have been corrected make this a major public health problem, with significant consequences for both the patient and community.

Two wake-promoting treatments have recently gained market authorization (MA) in France for this indication, offering a potential therapeutic option for thousands of patients, but also posing many practical questions for clinicians. How should these symptoms, which are often multidimensional and multifactorial in origin, be assessed? Which diagnoses and comorbidities should be excluded before prescribing these agents? How can the benefit-risk balance of the treatment be measured in those patients, often elderly, overweight or suffering from cardiovascular comorbidities? How can misuse of these wake-promoting agents be avoided? It should not be forgotten that modafinil, a wake-promoting treatment, which received approval to treat OSAHS in 2004 was withdrawn in 2010 due to the increased risk of psychiatric disorders (depressive disorders, suicidal ideation, psychotic disorders) and cardiovascular disorders, especially in patients with cardiac arrhythmia or uncontrolled hypertension (see SFRMS press release). Consequently, the *Société Française de Recherche et de Médecine du Sommeil* (SFRMS) and the *Groupe Sommeil de la Société de Pneumologie de Langue Française* (SPLF) decided to standardize clinical practices in France, to ensure the proper treatment for the proper patient, working with a group of French sleep experts across a range of specialties, pneumology, neurology, ENT and psychiatry. Several recent international journals have covered the issue, addressing the possible causes of OSAHS rEDS, differential diagnoses, listing investigation methods as well as the different drug treatments and their characteristics [5,27–30]. We believe it is important to understand, recognize and differentiate between: (1) the criteria applied to the clinical trials that led to market authorization (MA), (2) the precise wording of the market authorizations and (3) the recommendations and clinical common sense that expert opinions are based on. This article presents a detailed summary of the clinical practice recommendations for identifying and assessing EDS in this context, plus patient management and monitoring. A decision-making algorithm for management is proposed (Summary Fig. 1), as well as the situations in which a patient should be referred to a sleep center or sleep specialist, or sometimes to a center specializing in rare hypersomnias. These proposals are based on the current state of scientific knowledge at the time of the article's publication, based on a vote by all the authors on the proposals for which there was not 100 % agreement, and may be revised according to their evolution.

The recommendations are worded as follows:

- "**it is imperative**" means the measure must imperatively by applied to all patients (for safety or medico-legal reasons for example);
- "**it is recommended**" means the measure should be applied to most patients (example of an established effective treatment);



ABPM: Ambulatory blood pressure monitoring
AH: Arterial hypertension
BDI: Beck Depression Inventory
BP: Blood pressure
CBT: Cognitive behavioural therapy
CPAP: Continuous positive airway pressure
CV: Cardiovascular
EDS: Excessive daytime sleepiness
ESS: Epworth Sleepiness Scale
HAD: Hospital anxiety and depression scale
HR: Heart rate

IHSS: Idiopathic hypersomnia severity scale
MSLT: Multiple sleep latency test
MWT: Maintenance of wakefulness test
OHS: Obesity hyperventilation syndrome
OSAHS: Obstructive sleep apnea-hyponea syndrome
PHQ4: Patient health questionnaire
PLMS: Periodic leg movement during sleep
PSG: Polysomnography
RDI: Respiratory disturbance index
Tx: Treatment

Red flags: young subject, rapid weight gain, precocious puberty, severe EDS, dream activity during naps, sleep paralyses, sleep related hallucinations, cataplexies, severe inertia.

(1) Questioning is not reliable, difficulties distinguishing between EDS and fatigue, difficulties assessing the functional repercussions of EDS.

(2) Suspicion of concomitant sleep disorders potentially responsible for EDS.

(3) When the AHI was not severe (<30/h) before treatment of respiratory events.

Fig. 1. Management procedure for excessive residual daytime sleepiness in obstructive sleep apnea-hypopnea syndrome (OSAHS): a multidisciplinary, integrative approach. Six levels of assessment, management and follow-up of patients with residual excessive daytime sleepiness (rEDS) in OSAHS treated with continuous positive airway pressure (CPAP) are presented here, in concentric fashion. The starting point is the patient's complaint, hypersomnolence (in the center, in black). Then successively:- **Level 1** (blue): subjective assessment of the hypersomnolence and its severity; - **Level 2** (green): objective assessment of hypersomnolence and its severity; - **Level 3** (yellow): the various causes to be investigated. Note the different circles are of equal size since the etiologies can (and must) be investigated simultaneously by the sleep specialists; - **Level 4** (orange): management according to the cause. Again, actions should be taken simultaneously; - **Level 5** (pink): possible introduction of a wake-promoting treatment, after a complete assessment of levels 1, 2 and 3, and the management, if necessary, of level 4. Cardiovascular risk assessment is an integral part of this level; - **Level 6** (purple): Follow-up under medication. Note the 5 colored circles at the bottom of this last step (the colors refer to the levels) invite the sleep specialist to go through the previous steps again during the patient's follow-up. This approach provides a new kind of decision tree that is not a linear, not purely sequential. It is not a top-down clinical reasoning process, but rather it follows a multidisciplinary, integrative and concentric clinical reasoning process ("a decision blob"), where the levels complement each other and can be carried out simultaneously, repeatedly and dynamically during follow-up. *This figure was created by Cyrille Martinet - Illustrateur medical, Atelier 55, Bordeaux, France.*

- "**it is proposed**" means the measure can be applied to a proportion of patients (example of a very likely effective treatment);
- "**it is possible**" means the measure may be applied to some patients, although the available data do not allow definitive statement (example of a treatment of uncertain efficacy);
- "**it is not recommended**" means the measure should not be applied to most patients (example of an ineffective treatment);
- "**it is recommended not to**" means that the measure should not be applied (example of a treatment with an undesirable effect).

2. Prevalence and predisposing factors of sleepiness and residual sleepiness in OSAHS

OSAHS is a respiratory sleep-disorder characterized by the partial or complete closure of the upper airway during sleep, responsible for nocturnal intermittent hypoxia and sleep fragmentation, and associated with both nocturnal and diurnal symptoms [4,31]. The severity of OSAHS is usually based on AHI: mild (AHI of 5 to 15/h), moderate (15 to 30/h) and severe (> 30/h). And although the prevalence of OSAHS varies from one country to another, the current estimate is nearly one billion worldwide and rising, probably related to the growth in obesity in addition to healthcare workers and the general public now being more aware of the sleep disorder [32].

The complaint of EDS is one of the cardinal symptoms of OSAHS [6,33]. It comes with a major impact on quality of life, work productivity, mood, social and family interactions, cognitive functioning and risk of accident [11,34,35]. EDS in OSAHS patients is associated with a higher risk of road and domestic accidents [36,37] (even higher if the patient is unaware or only partially aware of their sleepiness [38]) and a wider prevalence of anxiety and depressive disorders [39,40]. Cognitive complaints are also frequent, including attention and executive functioning disorders, as well as memory complaints [19,41,42]. According to recent studies, including cluster analyses of large cohorts, subgroups of patients who were "excessively sleepy" compared with not very symptomatic patients, had a higher incidence of cardiovascular events and better cardiovascular risk reduction on CPAP [43,44].

Studies show that EDS is present in 41 to 77 % of OSAHS patients on initial diagnosis [45–48,8]. Other non-sleepy patients have complaints that are harder to quantify: nocturnal suffocation, a feeling of non-restorative sleep, fatigue or morning headaches, irritability, a sense of cognitive challenge and lower libido. The severity of the initial EDS is poorly correlated with the severity of the AHI [27]: EDS is worse in young people with a moderate rather than severe AHI, see below. The prevalence of initial EDS increases slightly (but significantly) with young age, female sex, high body mass index, reduced sleep efficacy, depressive symptoms, a depressive disorder and chronic pain [21]. Even so EDS is most often reversible once the respiratory event (apnea, hypopnea, respiratory effort) is corrected with an effective treatment. Prospective studies and randomized trials comparing CPAP or MAD with placebo show that CPAP decreases subjective (measured on the Epworth Sleepiness Scale) and objective (measured with the Maintenance of Wakefulness Test, MWT, or the Multiple Sleep Latency Test, MSLT) EDS in patients with moderate to severe OSAHS [49]. The more severe the OSAHS and the worse the EDS prior to treatment, the faster and greater the improvement in EDS on CPAP.

EDS may however persist despite optimal correction of respiratory events: this is referred to as residual EDS (rEDS) [11,15,23]. It is most often defined by a score of > 10/24 on the Epworth Sleepiness Scale. Few studies use objective measurement thresholds. There is no consensus on the amount of time post OSAHS treatment before rEDS should be evaluated. The authors of these articles do not consider the variability of subjective EDS measurement from day to day, even though it is well documented in the general population [50,51]. This parameter should be given consideration in future studies on the subject [5]. The prevalence of rEDS varies widely between studies, affecting between 9 and 55 % of patients depending on the definition used, and on the potential causes of the EDS (Table S1) [11,15].

For example, EDS persisted after 6 months in 55 % of 208 patients correctly ventilated with CPAP in a single center study [46]. Other studies suggest that the prevalence of rEDS is lower (< 20%), and some authors even consider that it is similar to the prevalence of EDS observed in the general population [9,16]. Many factors are associated with this prevalence (Table S1): the most robust are younger age, the presence and higher severity of the EDS prior to treatment, lower pre-treatment AHI, comorbidities (mood disorders, diabetes, cardiovascular disease and chronic pain) [46] and the duration of CPAP use. In a recent randomized trial, chronic pain and depressive symptoms were associated with a higher risk of rEDS, as well as the presence of a pre-treatment EDS [21], a result confirmed in other studies [11,12,17,26,21]. The prevalence of rEDS is 12 % to 55 % in patients who use their CPAP enough (more than 4 h/night for at least 70 % of nights) and lowers when use of CPAP increases [8,13,15,21,46]. In general, the prevalence of EDS is high during the first months of treatment and subsequently decreases. Hence the prevalence of rEDS gradually decreases with the length of CPAP treatment: many studies show a drop in rEDS between the 1st and 3rd month after treatment, and some longer studies a progression in benefit after 6 months of CPAP. These results are comparable with patients using a MAD [17]. In terms of duration of use, improvements in rEDS become apparent with an average of 2 hours of CPAP use per night, reaching satisfactory levels at 4 hours per night. Beyond this, further progress continues, leveling off between 7 and 8 hours per night [13,21]. The prevalence of rEDS is halved or even reduced by three quarters if other causes of sleepiness are eliminated [10,11]: in that case it's more common to talk about "unexplained" rEDS. In a French cohort of 502 patients with severe OSAHS followed in 37 centers, rEDS was present in 12 % of patients despite good CPAP compliance, and in 6 % of patients after considering factors associated with EDS like symptoms of depression, restless legs syndrome and sedative medication [11]. EDS is often explained by an accumulation of several factors in an individual. Fewer studies have characterized the clinical and electro-physiological phenotype with 24-hour polysomnography (PSG), MSLT and MWT in patients with unexplained rEDS, for whom sleep deprivation, a characterized depressive episode, symptoms of narcolepsy and the use of sedative medication had previously been excluded. These patients were more tired and reported more depressive symptoms and cognitive complaints than OSAHS patients without rEDS [14,19]. Objective measures of sleepiness are normal or subnormal in half of patients with rEDS. For example, MSLT latency was normal (> 8 min) in 90% of patients with unexplained rEDS, and subnormal (< 10 min) in 40 % of a French series; 95 % of patients had a non-extended sleep time (< 11 h) when measured over 24 h [14]. Only 15 % of patients with unexplained rEDS met the criteria for a central disorder of hypersomnolence, despite a high Epworth Sleepiness Score of 16/24. Prior to inclusion in a randomized trial to test modafinil, only 46 % of 50 Japanese patients with rEDS (Epworth Sleepiness Score >10) had abnormally low MWT values [20].

In an American study, 22 % of patients with CPAP treated OSAHS had an abnormal mean latency (< 7.5 min) on MSLT but used CPAP less (3.9 h/night) than those who normalized their MSLT [8]. In 29 patients with rEDS, MSLT latency was abnormal (< 8 min) in 31 % and subnormal (8–11 min) in 35% [25]. This suggests that the rEDS measured by the Epworth Score overestimates sleepiness compared with objective measures. Similarly, the almost constant memory complaint in these patients was not objectively corroborated either, since their performance on attention, executive function and memory tests

was within the norm [14]. This raises the problem of the existence of a sub-group of patients who are “dissatisfied with their state of health” (sleep, vigilance, cognition, mood, physical energy, mental energy) despite good ventilation, and whose overall complaint has no objective marker. Night-time sleep for patients with rEDS is often perceived as unrefreshing: with slightly less slow-wave sleep [14,17], and more non-arousing periodic limb movements. However there does not appear to be a connection between the presence of periodic leg movements at night and rEDS [7]. Results are comparable in patients using a MAD [17], but there are currently few studies on the subject.

Key points

- EDS is a cardinal symptom of OSAHS: it is associated with risk of accident, lower quality of life, mood disorders and cognitive impairment.
- EDS is often improved by correcting respiratory events (apneas and hypopneas, respiratory efforts) but can sometimes persist despite optimal treatment of OSAHS. This is referred to as residual EDS (rEDS).
- Residual EDS affects 6 to 55 % of patients with CPAP treated OSAHS, especially during the first few months of treatment, and then tends to decrease after 6 months of treatment.
- Residual EDS decreases with increased duration of nocturnal CPAP use.
- The complaint of sleepiness seldom correlates with objective measures of sleepiness (MSLT, MWT) and sleep latencies are often normal in rEDS.
- The risk of rEDS is greater when the EDS was already present and severe before initiating CPAP treatment.
- Younger age, a lower AHI at the time of OSAHS diagnosis and some comorbidities (depressive symptoms, cardiovascular disease, diabetes, chronic pain) are predictive factors for rEDS.
- Data on OSAHS rEDS seem comparable in patients using mandibular advancement device (MAD), but there are still few studies on the subject.

3. Pathophysiology of residual sleepiness in treated OSAHS

The pathophysiological mechanisms of rEDS in treated OSAHS are still not perfectly understood. They are probably multifactorial. rEDS may simply have another cause than OSAHS, and be incidentally associated with a high AHI: few studies of patients with rEDS (including an exhaustive work-up searching for another cause of EDS) have gone further than the questionnaire stage to look for a depressive disorder characterized by a psychiatric diagnostic evaluation, chronic sleep insufficiency (linked to poor sleep hygiene or a circadian disorder), nocturnal nasal obstruction (in the context of chronic rhinosinusitis) disturbing physiological breathing, a chronic illness that causes fatigue and sleepiness (inflammatory disease), impaired nocturnal sleep (periodic leg movements, slow wave sleep parasomnias, fragmented sleep due to pain, noise etc.) or central disorder of hypersomnolence. The negative correlation between AHI at diagnosis and the presence of rEDS on CPAP is an indirect argument supporting this hypothesis. This rEDS may also characterize a sub-group of patients with a general "complaint", more subjective than objective.

The work of Kingshott et al. also shows that there is little connection between objective sleepiness and sleep fragmentation (micro-arousals) in patients with OSAHS; only low oxygen saturation appeared to have a weak correlation with objectively measured sleepiness [52,53].

A hypothesis based on several animal studies suggests that chronic intermittent hypoxia and sleep fragmentation may induce oxidative damage to noradrenergic and dopaminergic neurons involved in the arousal systems or in connections between brain regions, after years without treatment (OSAHS often evolves quietly before being identified). This damage could be irreversible, thus explaining the persistence of EDS after the OSAHS has been managed. Exposure of rodents to chronic intermittent hypoxia for 6 months is associated with a 40 % loss of wake-promoting monoaminergic neurons [54], possibly related to the loss of white matter, altered neurons and microglia [55,56]. Similarly, after four weeks of sleep fragmentation, neuronal damage was found in areas that promote wakefulness [57]. However, there is little data on this in humans. A few studies have explored structural and diffusion MRI in patients with OSAHS [22,24]. A single diffusion MRI study showed alterations in white matter in patients with OSAHS and rEDS, but these patients had only recently been treated [22].

Patients with high blood pressure (BP) were excluded from the study, an important potentially confusing factor that should be considered in these imaging studies. The white matter changes observed before and after 3 months of CPAP treatment disappeared completely after 12 months of treatment [58], suggesting that these were reversible alterations in the diffusion MRI signal, which is sensitive to the movement of water in brain tissue and osmotic pressure. We must remain cautious and not over-interpret diffusion MRI data in OSAHS. Therefore, the role of intermittent hypoxic damage in the pathogenesis of rEDS has yet to be proven. Lower mean nocturnal oxygen saturation during sleep (but not AHI or desaturation index) has been shown to predict reduced MRI volume of the amygdala-hippocampus complex, thalamus, basal ganglia and frontoparietal cortex in 775 general population individuals [59]. These results also suggest that CPAP should be “given time” (12 months in this study) to fully demonstrate its benefit.

Key points

- The probable multifactorial origin of residual EDS in OSAHS makes its pathophysiological study difficult.
- A hypothesis based on animal models suggests that some cases of rEDS in OSAHS result from exposure to chronic intermittent hypoxia and sleep fragmentation, which induces irreversible oxidative damage to noradrenergic and dopaminergic neurons and neuronal circuits controlling wakefulness.

4. Assessment of sleepiness in OSAHS

4.1. Definition of sleepiness

The International Classification of Sleep Disorders (ICSD-3-TR) [60] defines EDS as the inability to remain awake and alert during the day, resulting in periods of an irrepressible need for sleep or involuntary episodes of sleepiness or sleep.

Hypersomnolence is comprised of several components to varying degrees [61]: EDS, prolonged sleep time (excessive amounts of night and day sleep) and symptoms of hybrid states between wakefulness and slow wave or REM sleep (for example: inertia on waking, automatic behaviors, slower psychomotor skills, mistakes due to inattention, hallucinations, sleep paralysis) [62]. We now know that a subject seemingly awake, with eyes open and involved in a cognitive task, may have slow waves in some brain regions, that could be “local sleep”. This condition has an impact on cognitive performance, behavior (slower, impulsive) and mental experience (focused, “mental blankness”, wandering thoughts) [63].

This article discusses only one component of hypersomnolence, EDS, which is the subject of the largest number of published OSAHS studies; but future studies could and should look at the other components of this symptom [64]. A special issue of the Revue Médecine du Sommeil [65] is devoted to the different approaches to pathological somnolence, its conceptual aspects and measurement tools. One

article describes the diversity of characteristics belonging to the different dimensions of hypersomnolence [66]. EDS is manifested by voluntary falling asleep (transient states that come and go within seconds [67]) in calm, passive situations and during monotonous tasks. EDS may be associated with impaired cognitive performance, including difficulties paying attention or a lack of responsiveness [68], thus sharing characteristics with fatigue, these dimensions are often partially intertwined and difficult to individualize in questionnaires [66].

Since the assessment and management of EDS and fatigue are different It is vital to distinguish clearly between them. Fatigue can be defined as the complaint of physical or mental exhaustion (leading to a reduction in cognitive and behavioral performance), associated with difficulty in initiating or maintaining voluntary activities, but which are not significantly improved by increased rest or sleep [69]. The clinician detects this exhaustion by asking about the reduced ability to carry out physical tasks such as cleaning, making a bed, walking, the need to rest, lie down and close the eyes, even without sleeping. The symptom of exhaustion is common in conditions such as depression, multiple sclerosis, cancer and insomnia. It is cardinal in a group of pathologies with variable diagnostic criteria: chronic fatigue syndrome, with or without fibromyalgia like pain (called “myalgic encephalomyelitis”), macrophage myofasciitis and prolonged persistent fatigue after a Borreliosis infection (“chronic Lyme disease”) or SARS-CoV-2 (“long covid”) [70]. Fatigue may also come with a psychological component. Fatigue can sometimes accompany EDS, accentuating the disability and its repercussions [69].

Apathy is another symptom sometimes confused with EDS: it refers to a lack of energy or motivation, often associated with a reduction in emotional response. In people with apathy there is a noticeable reduction in activities and spontaneous initiative. It may be associated with clinophilia, which is the almost constant desire to lie down, with longer periods spent in bed without sleeping, and should not be confused with EDS. Symptoms of apathy associated with lower mood can be found in characterized depressive disorder. Apathy is also a symptom in patients with neurodegenerative diseases such as Parkinson’s and dementia [71]. Assessing EDS is complex because of the possibility that it may be associated with fatigue, apathy, lower mood and clinophilia. The combination of these symptoms accentuates the disability and should not cause EDS to be underestimated in these contexts.

EDS is obvious on examination in some cases, disrupting work, daily life and driving. It may be observed during the interview: yawning, blinking, slower conversation, rolling eyeballs, falling asleep in front of the physician or in the waiting room, or on the contrary logorrhea and very rapid verbal flow as a countermeasure to stay awake. The patient may spontaneously complain of EDS. Sometimes EDS is less obvious: physicians need to know how to detect it. Some patients adapt very well to EDS, they develop avoidance or coping strategies, especially if it has developed gradually over the years. Others do not sense the EDS at all [72], which makes them a danger to themselves and others, especially when driving.

4.2. Subjective assessment of sleepiness

Interview

Several validated screening tools are available, but they are not a substitute for a full and detailed medical history. It is important to take the time to characterize the patient’s complaint, context, environment and sleep patterns before any further examination. The various elements that should be collected the medical interview to assess OSAHS hypersomnolence are listed in Fig. 2.

Sleep diary

A sleep and wake diary is an easy exercise and useful tool. Over a period of 2–3 weeks the patient records every day, bedtimes, wake times, estimated sleep time, nocturnal awakenings, naps and bouts of sleepiness during the day on a grid. The diary can be used to calculate mean sleep time/24 h, sleep efficiency, to detect chronic sleep insufficiency or, on the contrary, prolonged sleep time, and to identify mistakes in sleep hygiene and clinophilia. It is especially useful when the patient has a very irregular sleep pattern or when the interview is not reliable. Time must be taken to explain to the patient how to fill in the diary, and then analyze it with them. The *Réseau Morphée* (a French network) offers a diary and an explanatory note ("Agenda de Vigilance et de Sommeil"). In CPAP treated OSAHS the compliance report provides an indirect, partial indication of the nocturnal sleep diary, which is very useful: beyond CPAP compliance, irregular rhythms and nocturnal awakenings can be identified (Fig. S1). Moreover, an increasing number of patients now use connected watches and objects that measure activity/rest rhythms. These data can be useful for a sleep specialist, but they remain an indirect and imprecise reflection of sleep/wake rhythms; and these tools have yet to be validated in the context of OSAHS.

Self-assessment questionnaires

The main validated measurement tools for EDS are detailed in a recent review [66]. Some of these scales measure sleepiness at a given moment in time (Karolinska, Stanford and visual analogue scale) but they are typically used in experimental protocols and are of no use in the approach presented here. The other scales, described in detail below, measure hypersomnolence and its components over a much longer period (week, month). The Epworth Sleepiness Scale (ESS) is the most used in sleep medicine and therefore the most closely studied [73]. This self-assessment questionnaire, scored from 0 to 24, evaluates the subject’s propensity to doze off in 8 everyday situations, each ranging from 0 (“no chance of dozing”) to 3 (“high chance of dozing”). The internal consistency of this scale is satisfactory, as is its sensitivity to change and test/retest reliability [74]. It can be used as a screening scale (abnormal > 10) or as a severity scale to quantify and monitor EDS in clinical situations. A sleep physician using the ESS should however be aware of its limitations [75,76]. Patients might not understand the items (especially the difference between fatigue and sleepiness) or not experienced any of the situations recently (e.g.: driving, cinema, theater, a meeting): they must imagine the situation.

Question 8 (“in a car, while stopped for a few minutes in a traffic jam or at a red light”) intentionally does not specify if the patient is driver or passenger to make it equally applicable to non-drivers; explanation is necessary. The scale does not specify if the act of falling asleep is voluntary or involuntary either. Some patients are unable to evaluate their EDS and others may alter their responses for professional reasons. There is also little correlation between ESS scores and objective sleep latency (see Objective assessment of sleepiness) or accidental risk, hence the point of using scales that are specifically dedicated to accident risk (see below). The highest variability from one day to another or from one consultation to the next should be no greater than 2 points on the score: higher than that questions may be asked about its reliability. This is why we recommend measuring it several times before proposing an extensive EDS assessment or treatment. The scale should never be used on its own, it should always be combined with a detailed patient interview and, if in doubt, with family members. Since ESS mainly explores passive situations, reference centers often apply the sleepiness scale [77] to active situations, this assesses the risk of sleepiness from 0 to 3 in 4 active situations: driving, eating at mealtimes, working or performing a domestic activity (DIY, housework etc.): a score of >1/12 is abnormal.

Other scales than Epworth?

A validated psychometric tool can be used to assess the various components of hypersomnolence (EDS, longer sleep time at night and during the day, inertia on waking), and their frequency, duration and repercussions. This is the Idiopathic Hypersomnia Severity Scale [IHSS]) [78], validated in French. This self-assessment questionnaire

- Age at onset of symptoms, chronology in relation to diagnosis and initiation of OSAHS treatment
- Possible triggers: vaccination, infection, burn-out, changes in sleep schedule
- Habitual sleep-wake rhythm, weekdays and weekend: bedtime, wake-up time, sleep latency, number and duration of nocturnal awakenings. Complete with a sleep diary.
- Full list of medications, especially sedatives: doses and exact time of the day/night **(FIG. 3)**
- Consumption of alcohol, cannabis, psychotropic substances, tobacco, coffee **(FIG. 3)**: quantities and times taken.
- **Hypersomnolence:**
  - ➔ **Excessive daytime sleepiness (EDS)**
    - The patients may use different wording to describe their complaint: "need to sleep", "stinging eyes", "falling asleep", "lack of energy", "fatigue", "difficulty to concentrate", "exhaustion", "sensation of non-restorative sleep", etc.
    - Daytime naps, use the sleep diary: number, duration, time of occurrence, circumstances: monotonous activities, passive or active situation, scheduled naps, irresistible need to nap, refreshing or restorative character of sleep, associated dream activity, automatic behaviors (especially when the patient fights EDS; these behaviors are severe manifestations of EDS, altered states of consciousness during which more or less complex activities can be accomplished, with partial or complete amnesia).
    - Consequences: difficulties with concentration and memory, lack of responsiveness, impaired quality of life.
  - ➔ **Excessive duration of night and day sleep** over 24 hours: total sleep time averaged over weekdays and weekends, calculated using a sleep diary.
  - ➔ **Sleep inertia**: impaired cognitive and/or physical performance after wakening, prolonged time to regain normal cognitive functioning, maximum sleep inertia with inability to wake up alone, and sleep drunkenness with mental confusion on wakening.
- **Severity of hypersomnolence:** dangerous, irresistible sleep onset in certain circumstances, especially when driving, history of accidents or near-accidents *, high-risk occupation (drivers), lack of perception of the EDS (reported by family and friends, or demonstrated by an accident), automatic behavior, sleep drunkenness, significant disability, Epworth score >15.

- ***Red flags*** that suggest a central disorder of hypersomnolence **: young subjects (children, adolescents and young adults), rapid weight gain, precocious puberty, dream activity during naps, sleep paralysis, hypnagogic hallucinations (falling asleep), hypnopompic hallucinations (waking up), cataplexy, severe EDS, severe inertia. To learn more about these symptoms see the French *Protocole National de Diagnostic et de Soins (PNDS) Narcolepsies*.

- Comorbidities: psychiatric, somatic. Search for causes **(TABLE 1)**.

** Question to ask: "During the past year have you had at least one episode of severe drowsiness at the wheel, making driving difficult or requiring you to stop?"*
*** Refer the patient for evaluation to a French Center for Rare Hypersomnias* (see list)

Fig. 2. Questions to ask when assessing hypersomnolence in OSAHS. Hyperlinks: Sleep Diary, List of French Reference Centers, List of Frenc Competence Centers.

was initially developed for monitoring patients with this rare disease but could be useful clinically or in future studies for a broader standardized assessment of hypersomnolence. The Hypersomnia Severity Index (HSI) is another scale validated in patients with psychiatric pathologies, currently being validated in French [79,80]. The Sleep Inertia Questionnaire (SIQ) explores inertia in 4 sub dimensions: physiological, cognitive, emotional and behavioral [81]. Other self-assessment questionnaires for EDS can be listed [64,66], but these scales are not widely used, their psychometric properties are not well validated and their links with objective measures of vigilance have not been studied. The Resistance to Sleepiness Scale assesses the voluntary and involuntary propensity to fall asleep in situations where it is appropriate or not [82]. The Toronto Hospital Alertness Test (THAT) assesses alertness-related cognitive states and ZOGIM-A focuses on the functional consequences of sleepiness [83]. Questionnaires assessing overall sleep quality sometimes include questions relating to EDS and its consequences: the Pittsburgh Sleep Quality Index (PSQI) for example [84] evaluates sleep habits and quality over the previous month and includes two questions on EDS. The Leeds Sleep Evaluation Questionnaire includes items on the quality of wakefulness [85].

Assessment of accidental risk

Sleepiness assessment scales, and the ESS in particular, are inconsistently correlated with accidental risk [86]. Patients should be asked about their sleepiness when driving. The authors of this consensus recommend that at least one question be asked systematically. For example, an affirmative response to the question: "Over the past year have you experienced at least one episode of severe sleepiness at the wheel making driving difficult or forcing you to stop?" is associated with an increased risk of road accidents [87] (see Medicolegal consequences, driving). The Bordeaux Sleepiness Scale (BOSS) [88], a specific scale for measuring the risk of accident attributable to sleepiness, has recently been published. It provides a simple quantification of the risk of near accidents or accidents related to sleepiness at the wheel.

Fatigue and apathy scales

While hypersomnolence is increasingly well defined by sleep experts, fatigue remains a vague and poorly characterized concept, the standardized assessment of which is complex and controversial. That said, it is one of the symptoms listed in AASM criteria for the diagnosis of OSAHS [60] and decreases after OSAHS is treated with CPAP [89], more so with closer compliance and duration of CPAP use [90,91]. There are no fewer than thirty scales for assessing the symptom of fatigue [92,93]. These include the Pichot and Chalder fatigue scales, the Fatigue Assessment Scale (FAS), the Fatigue Severity Scale (FSS), the Multidimensional Fatigue Symptom Inventory, short form (MFSI-sf) and the Brief Fatigue Inventory. The Pichot and Chalder scales are among the most widely used in sleep medicine studies. The scores are often colinear to sleepiness scores but also depressive symptoms [15]. To date there is no objective assessment tool for fatigue. Standardized assessment of apathy is mainly carried out in neurological sleep medicine, with the Starkstein Apathy Scale. The Apathy Evaluation Scale (AES) is also used in this field [94].

Quality of life scales

Validated scales can be used to assess the impact of EDS on quality of life, its consequences and the disability it causes. Some of these self-assessment questionnaires relate directly to EDS like the Functional Outcomes of Sleep Questionnaire (FOSQ) which assesses the impact of sleepiness and fatigue on everyday activities and quality of life. There are long (30 item) and short (10 item) versions of the FOSQ [95]. Other scales are not directly concerned with subjective EDS but with quality of life in general: among the best known are the Euro quality-of-life (EuroQoL) questionnaire [96] and the SF-36 questionnaire [97].

Their use in the assessment of EDS in clinical practice is not clearly defined since they are often not very specific. That said, some of them are used as response-to-treatment criteria in therapeutic trials evaluating the efficacy of wake-promoting agents in rEDS. In clinical practice, the physician may simply ask the patient if the EDS affects their daily life and interferes with family, professional and social life.

Key points – Recommendations

Assessment of rEDS in a patient with OSAHS

- It recommended that a full and detailed history be taken (Fig. 2);
- It is recommended that the patient keep a sleep diary, ideally for two weeks (including one or two weekends), before considering a wake promoting treatment;
- It is suggested to use validated screening tools (self-assessment questionnaires), but they cannot replace face-to-face medical interview or a sleep diary;
- The Epworth Sleepiness Scale (and all subjective EDS scales):
  - It is recommended not to use them alone in the assessment of rEDS,
  - It is recommended not to introduce a wake promoting treatment straight away, regardless of scale scores, and even if these scores are high,
  - It is recommended that these assessments be repeated over time, one single measurement is often not sufficient;
- It is recommended that the risk of driving accident be systematically assessed in conjunction with EDS. It is suggested to ask specifically about the risk [(1)], or to use specific scales like the BOSS scale [88];
- Fatigue, apathy and clinophilia are symptoms that are qualitatively different from EDS but may be associated with it and aggravate the disability. It is recommended that these symptoms be assessed systematically, at least through interview; it is possible to use specific self-assessment questionnaires;
- It is suggested that the disability and quality of life associated with EDS should be assessed, to evaluate the severity then the reversibility/improvement with treatment.

[(1)] "Over the past year have you experienced at least one episode of severe sleepiness at the wheel making driving difficult or forcing you to stop?".

4.3. Objective assessment of sleepiness

Several tests are available to objectively assess sleepiness, prolonged sleep time or vigilance disorders. They are briefly described below.

4.3.1. Measuring sleepiness

The two objective measures of EDS conducted in routine clinical practice in sleep centers are the multiple sleep latency test (MSLT), which measures the ability to fall asleep, and the maintenance of wakefulness test (MWT), which measures the ability to stay awake. Recommendations for good clinical practice for these 2 tests have been published by the SFRMS (Fig. S2), and the AASM recommendations for their use were recently updated [98].

The MSLT is now the reference test for the objective measurement of sleepiness and tendency to fall asleep (Fig. S2). It was first validated in sleep deprived subjects then used to diagnose narcolepsy and subsequently applied to all forms of EDS. It measures the daytime tendency to fall asleep at fixed times every 2 h and looks for the presence of abnormal REM sleep onset (in the 15 mins following the 1st sleep epoch) [99]. With rEDS, the patient must use their CPAP or MAD for each nap [98]. Abnormal sleepiness corresponds with a mean latency of less than or equal to 8 mins. At the end of each test, it is important to record whether the subject thinks they fell asleep or not, which indicates their ability to perceive their own sleepiness. This test is only slightly influenced by the subject's own motivation and has a predictive value in the occurrence of accidents. [100]. A PSG recording of the night prior to the MSLT is compulsory: it validates that at least 6 h of sleep have been achieved and that respiratory events have been properly corrected, after verifying the subject's ventilation on the memory card/CPAP remote monitoring data for a period of at least 28 days before the MSLT. MSLT performs well in detecting narcolepsy and idiopathic hypersomnia with non-extended sleep time. It is disrupted (possible false positives and false negatives) by shift work and recent withdrawal from psychotropic drugs [101]. A French study showed that it was often normal in rEDS patients evaluated at the Rare Hypersomnia Reference Center [14].

The MWT measures the subject's ability to resist falling asleep and can therefore be classed as a tool for measuring alertness (Fig. S2). Unlike the MSLT it is not a diagnostic test. The MWT consists of resisting sleep for 4 daytime periods of 40 mins under standardized

conditions. There is no clear consensus on the average latency considered to be non-pathological, and several thresholds are used depending on the (professional or other) requirements as well as clinical judgement and the context. A patient with an average sleep latency of 19 min may be considered a high risk of accident, with a real risk of accident between 19 and 33 min [101]. At the end of each test, it is also important to ascertain whether the subject believes they have fallen asleep or not, which gives an indication of their ability to perceive their own sleepiness. There is also a motivational component (and therefore potentially falsifiable) that physicians must consider when interpreting the test. The MWT is used when EDS constitutes a public or personal safety problem, or to assess response to (CPAP, MAD, wake-promoting agent) treatment in somnolent patients.

In France the MWT is a medicolegal test required before professional drivers, especially those treated for hypersomnolence, can resume driving, according to the French law (Order of 18 December 2015, updated on 28 March 2022: *Order 28 March 22*, see Medicolegal consequences, driving). The MWT is also used in clinical practice to measure treatment effectiveness independent of the regulatory aspect. MSLT and MWT results for the same subject do not always concur (discordance in about 30 % of subjects) [98]. Other measures, such as pupillometry or evoked potentials are reserved for research purposes and currently have no place in the rEDS assessment of patients with OSAHS.

4.3.2. Measuring prolonged sleep time

Prolonged PSG recordings over 24 or 32 h in bed ("Bedrest" protocol) are used to quantify extended sleep time, especially in idiopathic hypersomnia [102]. Actigraphy is also interesting since it provides for indirect measurements over several days or even several weeks, but a long period lying down without sleep can mistakenly be qualified as hypersomnia, as in fatigue syndrome or some mood disorders. An excessive amount of sleep is defined as a duration of over 11 h/24 h on a continuous 24 h polysomnography recording (following an overnight stay at a sleep center and MSLT during the day) in the absence of sleep debt over the preceding weeks, or by a sleep duration of more than 19 h/32 h for the diagnosis of idiopathic hypersomnia [103]. However, this condition is quite rare in rEDS [14]. An indirect indication of an increase in sleep time is given by the CPAP compliance record. Hence, if CPAP is used for more than 10 h per 24 h the physician should look for a possible extension in sleep time (it should be noted that high use may be linked to use whilst alert, watching television for example).

4.3.3. Measuring alertness

Several validated cognitive and behavioral measures provide an objective assessment of alertness. But these tests are dependent on motivation and are potentially falsifiable. The Oxford Sleep Resistance Test (OSLER) does not use EEG: sleep latency is estimated behaviorally by a repeated absence of response to light stimulation (more than 21 s) during 4 sessions of 40 mins separated by 2 h [104]. The patient, in a semi-seated position, must remain alert and press a button in response to intermittent light stimulation. Latency decreases according to the time CPAP is used in patients with treated OSAHS and normalizes after one month of treatment [105]. Although this test measures attention and reaction time better than MSLT or MWT, useful for drivers, it is not currently the subject of a methodological consensus (there are no normal values).

It does not measure complex electrophysiological modifications associated with falling asleep, which sometimes come and go at second intervals [67].

The Psychomotor Vigilance Task (PVT) is one of the most widely used measures, but there is a lack of normative data for this test. It involves making a black square that appears on a screen at irregular intervals (from a few milliseconds to a few seconds) disappear by pressing a button. A dozen variables are recorded, including the average of the slowest 10 % responses and the number of missed signals (reaction time >500 msec). This measure of cognitive performance is a behavioral indicator of sleepiness. This test is also used in research to quantify waking inertia, particularly in cases of central origin of hypersomnolence [106–108].

The Sustained Attention to Response Task (SART) adds to the reaction test an attentional difficulty called Go/No Go: clicking on some signals and avoiding others. It also measures impulsiveness, of reacting too quickly. This is another interesting dimension of EDS, observed in children or people with attention-deficit/hyperactivity disorder (ADHD).

4.3.4. Pre-therapeutic assessment of residual sleepiness in OSAHS

As part of the pre-therapeutic assessment for prescribing a wake-promoting agent for rEDS in OSAHS patients, the authors of this consensus feel that a test to objectify sleepiness (MSLT or MWT) should be carried out in some circumstances and in response to some warning signs (see text below and Fig. 2). However, this recommendation needs to be qualified as opinions are divided among the experts: 55 % in favor, 40 % recommending that an objective test be carried out systematically, and 5 % with no opinion. It is important to remember that these tests are required to diagnose central disorders of hypersomnolence and prescribe wake-promoting treatments in these pathologies. They are also required in other conditions of secondary or comorbid hypersomnolence before prescribing a wake-promoting treatment. Prescription of a wake-promoting agent in a patient with strictly normal MSLT or MWT latency is very rare. Hence these tests are still very useful and informative, and of major importance in the diagnosis of a complaint of hypersomnolence, whatever the cause.

Key points – Recommendations

- Several tests are available to objectivize sleepiness (MSLT and MWT are the reference tests), but none are strictly speaking part of the "compulsory" pre-therapeutic assessment for prescribing a wake promoting agent for rEDS in OSAHS.
- Nevertheless, MSLT and MWT are of great importance in supporting the clinical, etiological diagnosis and severity of rEDS: they can guide clinicians' therapeutic choices. According to the authors of this consensus it is recommended that these tests be performed, at the very least, in the circumstances described below, and always preceded by polysomnography.
- To date there are no thresholds for mean latencies on MSLT or MWT for OSAHS rEDS that would lead to the immediate introduction of a wake promoting treatment, nor any contraindication to the prescription of such a treatment. That said, the authors of this consensus consider that in a patient with strictly normal tests (MSLT or MWT without any sleep onset), it is recommended that the indication for the treatment always be discussed in a collegial manner.

Before prescribing a wake-promoting treatment

- It is strongly recommended conducting MSLT in the presence of some *red flags*, raising suspicion of a central disorder of hypersomnolence (Fig. 2): young subjects (children, adolescents, young adults below 40), rapid weight gain (from a few months to a year), precocious puberty, severe EDS [(2)], dream activity during naps, sleep paralysis, sleep related hallucinations, cataplexy, severe inertia [(2)].
- MSLT is also suggested in the following circumstances:
- When it is difficult to assess EDS and its severity during clinical assessment: for example, when interview is unreliable (EDS is over or under-estimated, discrepancy between the patient's and their family's reporting of the complaint), difficulty in

distinguishing EDS from fatigue, difficulty in assessing the functional repercussions of EDS,
- When concomitant (comorbid) sleep disorders are suspected and potentially responsible for EDS (sleep fragmentation: parasomnias, periodic limb movements, restless legs syndrome, chronic pain),
- When the AHI is not severe (<30/h) before treatment of respiratory events (this situation should raise suspicion of another cause than OSAHS being responsible for EDS);
- MWT can be conducted to better characterize the rEDS and its severity, especially when rEDS constitutes a public or personal safety concern, depending on the clinician's judgement and access to the examination. MWT is not a diagnostic test, but it can provide a supplementary measurement in patients who do not wish to be treated and maintain high risk activities like driving.

After prescription of a wake promoting treatment

MWT has a medicolegal value in drivers who are sleepy or initially sleepy before treatment. The test provides objective information for French specialized physicians providing approvals for driving (see *Medicolegal consequences, driving;* Order Arrêté 28th March 2022). It is imperative to conduct MWT after CPAP or wake-promoting treatment in these drivers (who are sleepy or initially sleepy before treatment), to confirm that wakefulness has been restored and to renew their fitness to drive motor vehicles.

(2) **Severe EDS:** EDS with dangerous, irresistible sleep onset in some circumstances, such as driving, history of accidents or near-accidents, high-risk occupation, lack of perception of the EDS (reported by family and friends, or demonstrated by an accident), automatic behaviors. **Severe inertia:** sleep drunkeness, mental confusion on waking, clumsiness.

4.4. The different causes of sleepiness and their management

It is essential to conduct a thorough assessment of the causes of EDS present at the initial diagnosis of OSAHS, as future management will be based on it. It is important to adopt a clinical approach that avoids:

- systematically proposing CPAP for a high AHI;
- then systematically proposing a wake-promoting treatment if rEDS persists.

The possibilities of causes other than OSAHS for EDS must be considered from the outstart before prescribing CPAP. When a patient presents with several causes of EDS, it is not always simple to evaluate the contribution of each cause. Some causes can (and should) be diagnosed straight away and treated rapidly: narcolepsy, a major depressive episode and sleep deprivation for example. On the other hand, in the absence of an obvious cause, it is important to take the time to make a precise diagnosis before prescribing a wake-promoting agent, taking a step back (at least 6 months is often necessary). Broadly speaking there are six main causes to be considered (Table 1). Chronic sleep debt, in terms of frequency, is the first to be considered, followed by iatrogenic and toxic causes (Fig. 3), psychiatric causes (characterized depressive disorder), night-time sleep disorders (such as OSAHS), central disorder of hypersomnolence, and other medical causes. All these causes may be combined, and the diagnosis or identification of one cause should not prevent screening for the others (Summary Fig. 1).

5. Management of residual sleepiness in OSAHS based on its cause

Behavioral management of sleepiness: sleep debt

One of the most common causes of EDS in the general population is chronic behavioral sleep deficiency, which often works in synergy with other causes of EDS. The consequences of sleep debt are well known and include cognitive deficits, reduced alertness, impaired working memory performance and impaired executive functions. But there are significant differences between individuals, the determinants of which are still poorly identified. [109]. Sleep deprivation should be screened by interview, along with a sleep diary, CPAP report or even actimetry. For example, if the answer is inconsistent with the patient's sleep schedule item n°1 of the IHSS can be useful for screening ("What for you is the ideal duration of night-time sleep (during weekend or holiday for example)? 11 h or more; more than 9 h and less than 11 h; between 7 and 9 h; less than 7 h"). A situation that should give rise to suspicion of chronic sleep debt is a complaint of EDS in a patient who sleeps much longer at weekends than during the week (>1h30 difference). The main treatment is to extend sleep time (sometimes confirmed by the diary, CPAP reports, actigraphy) but this is not always easy to apply, depending on lifestyle and social and professional constraints. It takes at least one constraint free week (not just a weekend) to return to an "ideal" sleep pattern. This ideal sleep time is the subject of much debate since it varies so greatly between individuals (probably due to genetic factors), as well as within individuals, depending on age, environment and daytime activity. The distinction between a sleep-deprived (and therefore sleepy) long sleeper and a patient with a central disorder of hypersomnolence is sometimes difficult. A threshold of at least 10 h of sleep over 24 h, including at least 9 h during the night, has been proposed by European experts to define the excessive pathological need for sleep, but further data is needed to validate this threshold [69]. In this case the complaint must be associated with a disability directly related to poor daytime wakefulness which is not completely resolved by increasing sleep time. For average sleep time, the international recommendations (AASM, 2015) are 7 to 9 h per night for adults. Therefore, before any wake-promoting agent is prescribed, patients with OSAHS and rEDS who appear (even partially) sleep deprived should be offered an extension of sleep time, by extending the time spent in bed. The authors of this consensus consider that for the lower threshold, a sleep time of less than 6 h per night would appear insufficient in an EDS patient. Studies have shown that 6 h of sleep per night has a significant impact on performance after 14 days [109]. This sleep time is the minimum recommended for the performance of EDS MSLT [98] and used as an inclusion criterion in the therapeutic trials detailed below [110] (see Management of sleepiness with a wake-promoting agent).

Therefore, for patients with nighttime sleep <6 h, there is no validation of the efficacy of wake-promoting agents in randomized controlled trials.

Key points – Recommendations

- In patient with OSAHS with rEDS, it is recommended to look for sleep insufficiency through interview and sleep diary (and possibly actigraphy) before considering prescribing a wake-promoting treatment.
- Sleep of less than 6 h a night on average for one week or more should raise suspicion of sleep deprivation. It is recommended to increase patients' sleep time by extending their time spent in bed (7–9 h per night for two weeks), and to confirm this with a sleep diary (or indirectly based on the CPAP compliance report, or actigraphy).

Optimal management of OSAHS

The pneumology working group emphasizes that its objective was to generate simple answers to the questions clinicians deal with daily. The experts are aware that some proposals require the use of explorations/techniques that are not always available to the majority.

Table 1
List of the causes to look for in a patient with sleepiness complaint.

Causes	Details	Screening	Comments	Management
Chronic sleep insufficiency	Everyone has their own ideal length of sleep and can tolerate a moderate variation (of around −1h30). Circadian rhythm disorders and shift work can induce sleep debt. Sleep insufficiency is frequent and synergistic with other causes of sleepiness.	Interview, IHSS item n°1 may be useful for screening* (mismatch with patient's sleep schedule), sleep/wake diary, actimetry, CPAP use report	Situations that should alert the physician: - jobs with unlimited working hours - sleep >1h30 longer at weekends - improved daytime sleepiness during holidays Note that sleep requirements vary from one individual to another. A good week of unstressed sleep is needed to achieve an "ideal" sleep pattern	Extension of sleep time, to be confirmed by diary and/or actigraphy
Iatrogenic and toxic causes	Sedatives and toxic substances (alcohol, cannabis) can cause drowsiness, as can withdrawal from (or irregular use of) treatments and wake-promoting substances (caffeine, nicotine, corticoids).	Interview: list of treatments/ doses/ times taken; list of substances (use, abuse, dependence) quantities, times	Dopamine agonists, level 2 and 3 analgesics, antihistamines, benzodiazepines and many neuroleptics are sedative. Antidepressants can be sedative for some, but also mildly arousing or neutral for others (Fig. 3).	Adapt the dose, dosing schedule, change therapeutic class; organize a therapeutic or withdrawal window **
Psychiatric causes	Depressive disorder (most common), bipolar disorder, attention deficit disorder with or without hyperactivity. Other disorders and their treatments (anxiolytics, neuroleptics, sedative antidepressants, etc.): anxiety disorders, schizophrenic disorder, post-traumatic stress disorder, addictive disorders.	Extended interview, screening scales (HAD, PHQ4, or even BDI-II)	- The relationship between EDS and depressive symptoms is bidirectional, and it is sometimes difficult to determine whether EDS is a symptom of depression or depressive symptoms a consequence of EDS. - The chronology of symptom onset (e.g. first EDS then depression), patient history and impression can help guide diagnosis. A therapeutic drug test may also be useful.	- If psychiatric disorder confirmed: refer to a psychiatrist, prescribe antidepressants (prefer antidepressant classes that are more stimulating, to be taken in the morning) - If there is any doubt about a psychiatric disorder (especially when using screening scales): refer to psychiatrist for a diagnostic work-up
Night-time sleep disorders	Untreated nocturnal breathing disorder (or insufficient/inappropriate treatment), restless legs syndrome, periodic limb movements, parasomnias, insomnia.	Interview, telemonitoring data (compliance, AHI, leaks), technician's report (leaks reported by patient), CPAP polysomnography (with flow sensor independent of flow reported by machine)	- Any sleep pathology responsible for night-time sleep fragmentation can theoretically induce drowsiness. - Insomnia is more often associated with fatigue than real sleepiness.	Specific management of sleep disorders
Central Disorders of Hypersomnolence	Narcolepsy types 1 and 2, idiopathic hypersomnia, Kleine Levin syndrome, hypersomnolence secondary to neurological diseases: Parkinson's disease, Lewy body dementia, traumatic brain injury, myotonic dystrophy[a], multiple sclerosis, Prader-Willi syndrome [a], craniopharyngioma [a], brain tumors, post-viral hypersomnia [b]	Interview, polysomnography and MSLT, sleep assessment in a center specializing in central disorder of hypersomnolence, brain imaging if necessary	These pathologies are rare but still take too long to diagnose in France: it is therefore important not to miss the diagnosis. The Epworth score is often but not always >15/24. Around 1/3 of narcoleptic patients are obese, so it's easy to think of OSAHS before narcolepsy.	- Assessment and management in a center specializing in central disorder of hypersomnolence: refer patient to the List of French Reference Centers or List of French Competence Centers
Other medical causes	Metabolic or endocrine disorders (obesity, hypothyroidism, diabetes) renal or hepatic insufficiency, chronic inflammatory pathologies, cancers, chronic pain that fragments sleep, nocturnal nasal obstruction, chronic rhinosinusitis	Interview, clinical examination and assessment by a specialist. A minimal blood test including TSH, creatinine, transaminases, iron, blood count, bicarbonates and hs-CRP is recommended.	Many medical diseases can be associated with sleepiness, but the cause is not always clear. Management of these diseases must be optimized when assessing a complaint of EDS. One good examples is obesity, a very frequent comorbidity of OSAHS, and associated with EDS, independently of OSAHS. Comprehensive management is essential (dietary and exercise management) and in some cases bariatric surgery may be considered.	Specific management of the disorder

* IHSS item n°1: "What is your ideal duration of night-time sleep (during weekends or on holiday for example)? 11 h or more; more than 9 h and less than 11 h; between 7 h and 9 h; less than 7 h".

** See Fig. 3. Wake promoting and sedative treatments should be discontinued prior to diagnostic assessment.

[a] Diseases often associated with sleep disordered breathing and/or obesity.

[b] Reported after infectious mononucleosis, possibly after Covid-19 infection.

Abbreviations: BDI-II: Beck Depression Inventory Version II; HAD : Hospital Anxiety and Depression scale, AHI: apnea-hypopnea index, IHSS: Idiopathic Hypersomnia Severity Scale, OSAHS: obstructive sleep apnea-hypopnea syndrome, EDS: excessive daytime sleepiness, MSLT: multiple sleep latency test, PHQ4: Patient Health Questionnaire, CPAP: continuous positive airway pressure.

(+): slightly sedative; (++): sedative; (+++): very sedative; (+): slightly wake promoting, (++): wake promoting; (+++): very wake promoting

- All of these treatemnts / substances can influence alertness, and must be discontinued before a diagnostic workup (MSLT), long enough (at least 5 half-lives) before the test.
- Similarly, when assessing EDS, and rEDS in sleep apnea syndrome, the timing and quantity / dose of drugs taken must be carefully recorded, and always considered as potentially responsible (at least partially) for the patient's complaint (with sedatives the responsibility is often obvious, but the conditions under which treatments and wake promoting substances are withdrawn, and irregular consumption, must be considered). A therapeutic window can help answer questions about causality.

Therapeutic class / mechanism of action	Example of treatment / substances	Effect on alertness, sleep
Dopaminergic agonists	pramipexole, rotigotine, ropinirole	**sedative (++)**
Alcohol (GABA-ergic)	alcoholic beverages	**wake-promoting at low dose (+), sedative à forte dose (++)**
Alpha-2-delta ligands	gabapentin, pregabalin	**sedative (++)**
Central antihypertensives	clonidine	**sedative (+)**
Anticholinesterase agents	donepezil	No effect on alertness, but possible modification of REM
Antidepressants		
- SNRIs	venlafaxine, duloxetine	neutral or **wake-promoting (+)**
- SSRIS	fluoxetine, citalopram, escitalopram, paroxetine(1), sertraline	neutral or **wake-promoting (+)**
- Tricyclic antidepressants	clomipramine, amitriptyline, imipramine	**sedative (++)**
- Tetracyclic antidepressants	mianserine, mirtazapine	**sedative (++)**
- Selective catecholamine reuptake inhibitors	bupropion	neutral or **sedative (+)**
H1 antihistamines		
- 1st generation	doxylamine	**sedative (++)**
- 2nd generation	cetirizine, desloratadine	neutral ou **sedative (+)**
Antipsychotics (2)	loxapine, quetiapine, haloperidol, risperidone	**sedative (++)**
Baclofen	baclofene	**sedative (+)**
Benzodiazepines (GABA-ergics)	diazepam, lorazepam, alprazolam, clonazepam, clobazam, oxazepam	**sedative (+++)**
- Z-drugs	zopiclone, zolpidem	**sedative (+++)**
Cannabis	tetrahydrocannabinol	**sedative (+)**
Corticoids	prednisolone, fludrocortisone	**wake-promoting (++)**
Monoamine oxidase-B inhibitors	selegiline, rasagiline	**wake-promoting (+)**
Melatonin	melatonin compound, PR form (Circadin®), Slenyto®	**sedative (++)**
Adenosine modulators	theophylline, caffeine (3), theobromine	**wake-promoting (++)**
Nicotine (acetylcholine stimulation)	tobacco (4), electronic cigarettes (e-liquid with nicotine)	**wake-promoting (+)**
Opioids	morphine, methadone, fentanyl, buprenorphine, codeine, heroin	**sedative (+++)**
Wake-promoting agents, stimulants	- Dopaminergic wake-promoting treatments: modafinil, methylphenidate, solriamfetol, amphetamines	**wake-promoting (+++)**

Fig. 3. List of substances and treatments available in France that influence sleep, its architecture and alertness. NON-EXHAUSTIVE LIST. According to Krahn et al. J Clin Sleep Med 2021 [98]. **Abbreviations:** GABA, gamma-aminobutyric acid; SSRI, Selective Serotonin Reuptake Inhibitor; SNRI, Serotonin and Noradrenaline Reuptake Inhibitor; PR, prolonged release; SWS, slow wave sleep; REM, Rapid Eye Movements sleep.

	- Histaminergic wake-promoting treatments: pitolisant - Wake-promoting substances: cocaine, amphetamines	
Anti-epileptics (some are also used as mood regulators)		
	lamotrigine	**wake-promoting (+)**
	phenytoine, phenobarbital, levetiracetam	**sedative (++)**
	carbamazepine, topiramate, sodium valproate	neutral or **sedative (+)**
Sodium oxybate (GABA-ergic)	sodium oxybate [5]	**sedative (+++)**
Triptans	sumatriptan, almotriptan	**sedative (+)**

[1] Except for paroxetine: may be slightly sedative (+)
[2] Except for some 2nd generation antipsychotics: amisulpride and aripiprazole, neutral or slightly wake-promoting (+)
[3] Note that excessive consumption of caffeine is an exclusion criterion in most therapeutic trials testing the efficacy of wake-promoting agents
[4] Severe nicotine dependency can also disrupt sleep (e.g. a patient getting up regularly to smoke during the night)
[5] Treatment used in narcolepsy, taken in the evening and at night, which increases SWS (effective on several symptoms : sleepiness, cataplexy, disrupted nocturnal sleep)

Fig. 3. Continued.

Working with multidisciplinary networks must be encouraged and developed for patients to access to these explorations and techniques. The pneumology working group would also like to reiterate the importance of assessing sleepiness before introducing CPAP. To be considered rEDS the EDS must have existed prior to the introduction of CPAP.

Despite the development of alternative treatments, in 2022 CPAP is still the reference treatment for symptomatic patients presenting with severe OSAHS and for patients with moderate OSAHS in some indications (HAS 2014 guidelines and JO Dec 2017). It is estimated that more than 1.6 million patients are fitted with CPAP in France. In 2019 the AASM meta-analysis of 38 randomized controlled trials in 7462 patients with moderate to severe OSAHS showed a significant reduction in sleepiness on the Epworth Sleepiness Scale on CPAP (mean reduction of 2.39 points for a 95 % confidence interval of 1.90 to 2.88) [111]. Limited to sleepy patients (defined by an Epworth score of >10, i.e. 6197 patients in 33 randomized controlled trials) the reduction was 2.71 points (95 % confidence interval of 2.15 to 3.27) [111]. It should be noted that in this meta-analysis significant improvements were seen on MWT and Osler tests (752 patients; 7 randomized controlled trials), but not on MSLT (442 patients; 7 randomized controlled trials [111]. With the efficacy of CPAP on sleepiness (especially subjective sleepiness) confirmed, what does optimized management of CPAP in a patient before prescription of a wake-promoting agent mean?

Equipment related problems must always be considered when a patient with CPAP treated OSAHS presents with rEDS. Meticulous assessment of the three quality factors of CPAP treatment is therefore essential:

- Assessment of compliance with CPAP therapy, related to the patient's actual sleep time, not limited to the "administrative" threshold of 4 h;
- Assessment of CPAP efficacy on the sleep breathing disorder, not limited to residual AHI measured by AHI flow;
- Assessment of CPAP tolerance, presence of side effects related to the CPAP, ventilation interface, sleep interruption and/or prolonged bouts of wakefulness caused by CPAP, which entail interactions between the clinician, the health technician and the patient.

Quality of CPAP treatment: compliance?

CPAP compliance conditions its effectiveness. This has been clearly demonstrated for daytime sleepiness, with an observable benefit from 2 h and increasing with a plateau observed in study populations of between 7 and 8 h per night [8,21,13]. The working group stresses that, in practice, a universal hourly threshold is meaningless for clinicians; the objective is to achieve CPAP compliance as close as possible to the patient's actual sleep time. CPAP compliance cannot be the same for a patient sleeping 4 h a night compared to another sleeping 8 h a night. Bearing in mind the recommended sleep duration in the general population (7 h/night) the working group considers that for the majority of patients CPAP use of at least 6 h is desirable on most nights (80% for example), at best every night.

While the average duration of compliance per night is an essential variable in assessing the efficacy of CPAP equipment on EDS, the time from initiation of CPAP therapy is also a decisive variable. As previously mentioned, most studies evaluating the evolution of the prevalence of EDS in treated patients are observational, with follow-up ranging from 3 to 24 months, and report a variable prevalence of rEDS [5]. Controlled EDS is often only achieved after 3 months of treatment with benefit increasing up to 6 months of treatment and beyond [21,26]. A multicenter randomized controlled trial evaluated rEDS monthly during the first 3 months of CPAP use and showed a progressive decrease in its prevalence from 60 % to 17 % (despite the persistence of significant sleep disturbance during CPAP treatment documented by actigraphy) [18]. In patients with CPAP treated OSAHS for whom CPAP treatment has recently been initiated, after elimination of some causes that must be diagnosed at the outset (e.g. sleep deprivation, narcolepsy, characterized depressive episode, see below), the working group proposes that a rEDS diagnosis should not be brought up before at least 6 months of CPAP treatment: 3 months to optimize management (pressure settings, choice of ventilation interface, adaptive measures such as adding a humidifier, heating circuit, habituation of patient and partner), then 3 months to assess efficacy (see below).

Quality of CPAP treatment: CPAP efficacy on sleep disordered breathing?

Various professional bodies have taken a position on the questions of "how to measure" the effectiveness of CPAP and "which reference test to use".

How to measure the efficacy of CPAP?

The working group points out that since the American Thoracic Society recommendation in 2013, most CPAPs available on the market use an efficiency index called AHI flow [112]. In the era of telehealth and given the patient population to be assessed it is tempting to consider this index as a substitutable value for AHI measured by polygraphy (RP) or PSG. Unfortunately, strictly speaking AHI flow cannot be superimposed on the AHI measured by RP or PSG for definition related reasons:

- AHI flow measurement does not include any measurement of desaturation or micro-arousal [112], it is only a measurement of flow, by definition;
- for industrial reasons, "apnea" and "hypopnea" definitions are manufacturer specific [112–114], making comparisons between different manufacturers' AHI flow impossible [115], in a highly competitive sector where it is in the manufacturer's interest to report the lowest AHI flow. Moreover, in the event of major leaks the AHI calculated by the algorithm will be impossible to interpret.

Beyond these limitations the AASM's 2021 recommendation [116] is to propose home titration of CPAP in auto-CPAP mode as the first line treatment for patients with no comorbidity, especially cardiovascular comorbidity. But this titration is insufficient in symptomatic patients and the AASM recommends monitoring CPAP with RP/PSG. A patient presenting with rEDS is symptomatic: the effectiveness of CPAP should therefore be verified by polysomnography before prescribing a wake-promoting agent with the rEDS indication.

For CPAP recording, there is no French consensus about the origin of the flow to be used to score events. The 2008 AASM consensus suggests using either the machine flow rate (then reintegrated into the RP/PSG recording) or an independent flow sensor coupled with the RP/PSG (with the choice of linearized or non-linearized flow rate, see below) [117]. The 2012 AASM consensus [118] based on expert opinion, favors using machine flow, which now seems inappropriate considering the published literature along with the inability of CPAP machines to identify respiratory related arousal leading to micro-arousal or respiratory effort related arousal (RERA) highlighted by the American Thoracic Society in 2017 [119,120].

CPAP machines have a linearized signal to compensate for the turbine's undesirable effect on the flow, the pneumotachograph alternative being economically incompatible with the current selling price of a CPAP machine. The linearization of a flow signal consists of applying a square root transformation, which results mathematically in a reduction in the amplitude variations of the signal. Since our definitions of respiratory events are based on decreases/modifications in signal amplitude, this linearization can therefore lead to events not being coded when desaturation or micro-arousal exists. This point has been specifically emphasized and detailed by the American Thoracic Society's working group on flow limitations, with the group deciding in favor of a non-linearized flow during the initial diagnosis [120]. The clinician must keep in mind that a linearized flow rate like that of a CPAP machine will result in a loss of sensitivity in diagnosing smaller amplitude events like hypopneas and flow limitations [121]. To avoid this, the authors of these guidelines recommend the use of a flow sensor independent of the CPAP, allowing the clinician to include a non-linearized flow in the PSG.

Which reference index should be used?

Various learned societies have taken a clear position on the reference index to be used when assessing the efficacy of CPAP treatment. Rather than the AHI it is the Respiratory Disturbance Index (RDI) measured by PSG. The RDI can only be measured by PSG since it is defined by the sum of the AHI and the RERAs per hour of total sleep time. In practice, flow limitations associated with respiratory effort are counted as RERAs but are not exclusive to RERAs, and the clinician must bear in mind that their sensitivity is imperfect: some episodes of RERAs identified using an esophageal pressure or probe or EMG are not associated with flow limitations [122–124]. In 1998 Meurice et al. [125] compared the efficacy on MWT of CPAP titration under PSG compared to auto-CPAP mode on flow limitations in a population of patients newly diagnosed with OSAHS. PSG titration provides better correction of MWT than auto-CPAP mode. In the only study published to date comparing the accuracy of CPAP RERA flow to RERA measurement during PSG, the correlation was only 0.10 (p = 0.22) [119]. The authors of this consensus recommend that PSG should be performed systematically with CPAP, as part of the rEDS assessment.

The AASM and the German Society of Sleep Medicine consider an RDI < 5/h during PSG on CPAP to be the objective [117,126]. The development of new effort measurement technologies (tracheal sound/sternal pressure, mandibular movement, pulse transit time, electromyography) will make it possible to increase the diagnostic performance of PSG with the implementation of these signals in the PSG [127]. At the time these recommendations were drafted the working group was unable to take a position on the signal (or signals) to be used.

Quality of CPAP treatment: CPAP-related side effects?

CPAP treatment may cause side effects associated with sleep fragmentation, which might facilitate rEDS.

Adjustment of the CPAP control mode (autopilot versus constant pressure) has not been found to be a factor in subjective (meta-analysis of 19 randomized controlled trials / 1390 patients) or objective (meta-analysis of 6 randomized controlled trials / 593 patients) rEDS [111]. The working group would like to qualify the results of this meta-analysis by pointing out that, depending on the CPAP pressure increase and decrease algorithm, sleep fragmentation in autopilot mode can be observed, with a sleep efficacy negatively associated with pressure variability [128]. Therefore, in patients on self-controlled CPAP, it is recommended to ensure that there is no sleep fragmentation caused by pressure variations in the device. In this case it is recommended to switch to fixed pressure followed by a reassessment of sleepiness symptoms.

The interface used is another source of side effects potentially associated with a complaint of sleepiness. Side effects can lead to increased sleepiness because not only do they lower CPAP compliance but also cause sleepiness fragmentation per se. As early as 1999, Teschler et al. reported an association between sleep fragmentation and mouth leaks [129]. The impact on sleepiness does not seem to be linked to the type of interface but to the side effects of the device. In the 2019 meta-analysis of 2 randomized controlled trials involving 57 patients and comparing facial interface with nasal interface, there was no difference in subjective sleepiness (Epworth score) [111]. In a real-life study of 1484 patients treated long-term (25 % for more than 9.7 years), the type of interface was not a significant predictor of subjective rEDS (Epworth > 10 in 16.17 % of patients) in the multivariate regression model [130]. On the other hand, the presence of patient reported leaks and side effects such as complaints of a dry nose or noisy mask were associated with rEDS. The existence of a dry mouth (which may be the consequence of mouth breathing) was also reported to be associated with rEDS [15]. In the study by Rotty et al. [130], the impact of CPAP side effects appeared to be independent of the duration of CPAP use. It is also worth noting that in the same

study, machine reported AHI flow and machine reported leakage data had no impact on rEDS. This is counterintuitive for leakage but in long-term treated patients, machine and patient reported leakage data are uncorrelated [130,131]. This is probably because patients who initially perceive significant leakage causing discomfort will not continue with CPAP. These patients are probably not evaluated in these long-term real-life studies because they have discontinued CPAP. For these long-term treated patients machine data is therefore of limited, if any, help and may be falsely reassuring.

Patient/home healthcare provider (HHP) interaction is necessary in identifying and resolving these side effects. A SPLF/SFRMS working group recently proposed a decision tree with action to be taken by the HHP regarding the various alerts generated by remote monitoring [132]. It should be remembered that CPAP treatment is a medical prescription, carried out by the HHP in accordance with the legislative text of 16 December 2017.

In patients with unresolvable CPAP side-effects, and for whom CPAP itself has created side-effects affecting the quality of sleep, or when treatment compliance is a problem, MAD should be considered as an alternative [133]. A specialist ENT opinion may then clarify the anatomical phenotype, diagnose and treat the nasal obstruction responsible for poor interface tolerance [134,135], and investigate the causes of high CPAP pressure when using autopiloted mode, suffocation on CPAP or the presence of residual events (which may be cases of epiglottic tilting). An alternative treatment to CPAP can be considered if optimization has not been achieved by the end of the treatment. MAD should be considered, requiring a minimum pre-treatment assessment (dental panoramic and dentist's opinion on a contraindication to MAD). If a previous treatment has failed, the patient may be offered induced sleep endoscopy. This helps to understand the reasons for the failure, and to propose alternative solutions to CPAP such as MAD, neurostimulation, or even a surgical option if there is no contraindication during the induced sleep endoscopy (such as the visualization of a concentric collapse of the velum for example) (see French 2022 recommendations SPLF/SFORL/SFAR/AFSORL [133]).

Key points – Recommendations

- Before the prescription of a wake-promoting agent, it is recommended that the clinician thoroughly assess the 3 quality factors of CPAP treatment which are therapy compliance, CPAP effectiveness, and absence of CPAP side effects.
- Machine data from remote monitoring showing AHI flow<5/h and an absence of unintentional leaks are not sufficient to consider prescribing a wake-promoting agent. It is recommended to see the patient in consultation, to interact with the HHP that manages the CPAP settings, technical aspects and comfort (interface, humidifier) and to carry out a polysomnography with CPAP.
- Patient compliance:
  - It is recommended to achieve therapeutic compliance as close as possible to the patient's sleep time (after having eliminated concomitant/comorbid factors of non-respiratory sleep disorders and insomnia and/or sleep debt in particular). For most patients, an objective of more than 6 h/night is a desirable minimum, on most nights, at best every night;
  - It is recommended to wait a minimum of 6 months: 3 months to optimize the settings and/or the side effects of CPAP, then 3 months of optimized treatment.
- Effectiveness of CPAP on sleep-disordered breathing:
  - It is recommended not to rely on AHI flow to consider that CPAP is effective in a patient with rEDS. It is recommended that the effectiveness of CPA be verified systematically by PSG, with a specific non-linearized flow measurement during PSG (measurement independent of CPAP flow),
  - For CPAP to be considered effective, it is recommended that a RDI < 5/h be obtained during PSG.
- Absence of CPAP side effects:
  - In patients on self-controlled CPAP, it is recommended to ensure that there is no sleep fragmentation caused by variations in the pressure of the device [(3)]
  - It is recommended to assess whether the CPAP itself is not affecting the patient's quality of sleep (poor tolerance, discomfort, leak, noise etc.),
  - It is recommended that the adverse effects of CPAP treatment reported by the patient should be managed: percutaneous leakage, nasal dryness and mask noise should be limited as much as possible,
  - It is recommended to look for nasal obstruction, responsible for mouth breathing, high pressure and possible unintentional leaks at the interface,
  - A specialist ENT opinion should be sought to restore physiological nasal breathing during sleep (which contributes to good quality sleep) and determine the anatomical phenotype of the OSAHS,
  - It is recommended not to rely on machine leakage data to explain rEDS. Only patient reported perception of the leak is associated with rEDS.
  - It is recommended to evaluate the possibility of a therapeutic alternative to CPAP such as MAD, positional therapy, hygienic and dietary rules, radical or functional surgery for the primary treatment of OSAHS before prescribing a wake-promoting agent.

[(3)] In this case, switching to fixed pressure is recommended, followed by a reassessment of the symptoms of sleepiness.

Optimal management of comorbid psychiatric disorders

Many of the comorbid psychiatric disorders of OSAHS may be associated with (and are sometimes responsible for) EDS: mood disorders (major depressive disorder, bipolar disorder), anxiety disorders, attention deficit disorder with or without hyperactivity, schizophrenic disorder, post-traumatic stress disorder and addictive disorders. Characterized depressive disorder is certainly the most common of these, with 48 % reporting EDS during a characterized depressive episode [136]. This disorder is thus one of the most frequent causes of EDS in the general population. The bidirectional relationship between EDS and depressive symptoms sometimes makes assessment difficult. EDS may in fact be a symptom, or even a prodrome of a characterized depressive disorder, or depressive symptoms may be a consequence of EDS [136]. In addition, the EDS of patients with OSAHS is associated with a higher prevalence of characterized depressive disorder and anxiety disorder [39,40], and characterized depressive order itself is associated with a higher risk of rEDS [21]. It should also be stressed that characterized depressive disorder and OSAHS may share some symptoms: attentional difficulty, irritability, weight gain, psychomotor disorders. OSAHS is an aggravating factor (or a factor in treatment failure) in a characterized depressive episode. All patients treated for OSAHS should therefore be screened for psychiatric comorbidities and treated if necessary. There are several screening scales for anxiety and depressive disorders such as the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR16) [137], the Beck Depression Inventory (BDI) for depressive disorder, the Generalized Anxiety Disorder (GAD-7) [138] for generalized anxiety disorder, the Hospital Anxiety and Depression Scale (HAD) [139] and the Patient Health Questionnaire (PHQ-4) for both disorders [140]. The HAD and PHQ-4 have a sensitivity and specificity of around 80%, which is very satisfactory for anxiety and depressive disorders, and their use is recommended by the SFRMS [141]. The HAD scale was designed to screen for anxiety and depressive

disorders, specifically to avoid confusion with symptoms of fatigue, somnolence or insomnia. It is therefore a useful screening tool for sleep medicine. Each item is rated by the patient from 0 to 3, with 7 items for anxiety (total A) and 7 for depression (total D). The thresholds are as follows for each of the scores (A and D): < 8, no symptoms; 8 to 10: subclinical (mild) symptoms; > 10: clinically significant symptoms that should lead to a diagnostic psychiatric evaluation. The PHQ-4 scale is a very short psychiatric screening tool for generalized anxiety disorder and depressive disorder. It combines items from the GAD-7 (screening for generalized anxiety disorder) and PHQ-9 (screening for depressive disorders) scales. Each item is rated by the patient from 0 to 3, with 2 items for anxiety (total A) and 2 for depression (total D). The thresholds are as follows for each of the scores (A and D): a score > 2 suggests a generalized anxiety disorder or a depressive disorder. Suicidal ideation can be looked for during interview, the Columbia-Suicide Severity Rating Scale (C-SSRS) is used to determine the risk and existence of current or past suicidal behavior. The C-SSRS can be used both clinically and in research and was selected by the Delphi study constituting the set of assessments for the SoPsy-depression national cohort of the French SFRMS and AFPBN societies [141].

The Beck Depression Inventory Version II (BDI-II) is often used in therapeutic trials (see Management of sleepiness with a wake-promoting treatment), as an exclusion criterion above a certain score [142]. This self-assessment questionnaire, validated in French, detects the presence and severity of depressive symptoms over the last two weeks. There are 21 items, each with 4 possible responses (scores 0, 1, 2 or 3), with higher scores indicating more severe symptoms (score total 0−13 = no or minimal symptoms; 14−19 = moderate severity; 20−63 = moderate to severe depressive symptoms). Item 9 concerns suicidal thoughts (a score > 1 indicates the presence of suicidal thoughts). However, this scale can be criticized because it contains one item on sleep and another on fatigue; which makes the symptoms “co-linear” and hard to distinguish. Lastly, the QD-2A scale, known as the “Pichot scale” [143] is “historically” often mentioned in sleep medicine in France. Although psychometrically of interest it is little used and seldom mentioned in international studies, making international epidemiological comparisons difficult.

All these questionnaires are commonly used in clinical trials because they allow for standardized assessment, but they do not diagnose a characterized depressive episode or an anxiety order. They are screening tools for clinical practice and a patient should be referred to a specialist for confirmation, according to the international ICD-11 or the DSM-5 [144] diagnostic criteria. Clinical psychiatric evaluation and history enable clinical diagnosis of a characterized depressive episode to be made, according to international DSM or ICD diagnostic criteria. The intensity of depressive symptoms can be assessed using the depression scales mentioned above, as can the follow-up and therapeutic response to antidepressants. Preference should be given to the classes least likely to cause sleepiness, to be taken in the morning (Fig. 3). Psychiatric disorders are often treated with agents that may induce EDS, such as anxiolytics and some sedative antidepressants (Fig. 3), and their indications, doses and dosing schedules must be systematically reconsidered as part of the assessment of rEDS in a patient with OSAHS. It should also be emphasized that these treatments can have an influence on states of alertness and should be stopped before a diagnostic workup (MSLT), long enough (at least 5 half-lives) before the test, according to international recommendations [98]. Antidepressants also affect sleep patterns: long-term use or withdrawal may result in REM sleep suppression or rebound (occurrence of REM sleep onset) [145].

Occasionally a patient with EDS may present with depressive symptoms but without a characterized depressive episode. The chronology of the onset of symptoms (e.g. first EDS, then depressive symptoms) may guide the sleep specialist in making a diagnosis [146]. That said, a specialist psychiatric opinion is always useful, and even necessary for these patients.

Prescription of a wake-promoting agent (see Management of sleepiness with a wake-promoting treatment) in a patient with a psychiatric disorder (characterized depressive disorder, bipolar disorder, anxiety disorder or psychotic disorder) comorbid with EDS must be conducted in consultation with psychiatric management. Comorbid psychiatric disorders must be treated with specific drug therapies, in efficient doses, and monitored regularly. Wake-promoting agents may increase depressive symptoms but are generally well tolerated (modafinil [147,148], methylphenidate [148−150], pitolisant: studies available only in populations of narcoleptic patients [151,152], and solriamfetol: study available only in patients with stabilized depressive symptoms [153]) and may even improve residual depressive symptoms [154,155]. It should be noted that modafinil and methylphenidate appear in international recommendations as treatments that can be used in characterized unipolar or bipolar depressive episodes, when response to a mood regulator drug is partial (with or without EDS) [154,155]. The appearance of anxiety symptoms, agitation, suicidal ideation or delusions is possible but remains rare [147−153]. However there is a lack of tolerance data specific to these populations. Anxiety symptoms should be monitored in patients with anxiety symptoms, which may worsen when wake-promoting agents are introduced, or doses increased.

Attention deficit disorder with or without hyperactivity (ADHD) in adults is worth mentioning, as the prevalence of hypersomnolence is high in this condition [156]. It can be screened using the Adult Self-Report Scale Short version (ASRS) or the DIVA 2.0 diagnostic interview guide, but the formal diagnosis must be made by a psychiatrist.

Chronic insomnia (falling sleep, staying asleep, or early waking) with or without comorbidity is one of the most common sleep disorders, but is rarely responsible for daytime sleepiness: that is more a question of fatigue [157]. When CPAP is poorly tolerated (leaks, too much pressure), it may also be responsible for a complaint of insomnia. Diagnosis is based on face-to-face interview and may be supplemented by a sleep diary. Severity is assessed using scales such as the Insomnia Severity Index (ISI) [158]. The daytime consequences of this disorder are multiple: cognitive and emotional complaints, fatigue, impairment of daytime functioning and quality of life. The short sleep duration form of insomnia (this phenotype is not the most frequent) may be responsible for a certain amount of sleep debt [159]. Treatment of chronic insomnia is based on cognitive behavioral therapies (CBT) [160], and in some cases on treatment of the cause (e.g. restless legs syndrome).

Optimal management of comorbid circadian rhythm disorders

Circadian rhythm disorders should always be investigated as part of the rEDS assessment: phase advance or delay, shift work, night work, jet lag. A lack of circadian alignment with the day-night cycle can lead to EDS. Phase delay syndrome and social jet lag are particularly common in this context, especially in adolescents and young adults, and can be assessed using the Munich Chronotype Questionnaire (MCTQ) [161]. Medical interview, as well as a sleep diary, CPAP use report and even actigraphy are all useful tools for assessment. The Horne&Ostberg circadian typology questionnaire is used to determine the chronotype, i.e. sleep schedule preference: and is interpreted as follows: score above 70: subject a morning person, 59−69: moderately a morning person, 42−58: neutral, 31−41: moderately an evening person, below 30: an evening person. This chronotype must be known as part of the assessment and management of a patient with OSAHS and rEDS, as well as the patient’s environment and sleep/wake rhythms, so that they can be optimized before any wake-promoting agent is prescribed. Some professions are particularly at risk, and screening for circadian rhythm disorders is essential for pilots and professional drivers. Treating circadian disorders

requires behavioral measures, and sometimes prescription of light therapy or melatonin (see SFRMS recommendations on the treatment of circadian rhythm disorders) [162].

Key points – Recommendations

Assessing rEDS in an OSAHS patient:

- It is recommended that, before considering a wake-promoting treatment, a depressive and/or anxiety disorder and/or a bipolar disorder and/or a psychotic disorder should be looked for.
- Medical interview and screening scales (HAD, PHQ-4) can raise suspicion of a characterized depressive episode, the diagnosis of which must then be confirmed by a psychiatric evaluation. It is suggested that these scales be used for assessment, but there is no threshold for these self-assessment questionnaires that would formally contraindicate the prescription of a wake-promoting treatment. However, scores of anxiety or depression on the HAD>10 or PHQ4>2 should alert the physician and prompt referral to a psychiatrist.
- In some cases, it may be possible to prescribe a wake-promoting agent and a psychiatric treatment simultaneously, but this should only be considered after seeking the opinion of a psychiatrist, and together with regular monitoring alongside psychiatric care.
- It is recommended that circadian rhythm disorders be investigated and treated before prescribing a wake-promoting treatment.

Optimal management of comorbid neurological disorders

Numerous neurological pathologies comorbid with OSAHS may be responsible for EDS: central disorder of hypersomnolence, myotonic dystrophy (Steinert's disease) [163], Parkinson's [164], Alzheimer's [165], stroke, multiple sclerosis [166], head injuries and hypothalamic dysfunctions.

EDS appears to affect between 16 and 50 % of Parkinson patients, although it is rarely detected by MSLT. It appears to be related to the severity of the disease, but may precede it by several years, and often worsens with the introduction of dopaminergic agonist treatments. In 1 to 14 % of patients, sudden onset of sleep may also occur, without prodrome and often in an active situation, exposing the patient to risk of accident. Dopaminergic treatments may be responsible for these sleep attacks, as well as benzodiazepines and other psychotropic drugs. However, several other pathophysiological mechanisms are probably involved in this EDS: reduced amplitude circadian rhythms, OSAHS, excessive fragmentation of night sleep and degeneration of hypocretinergic and monoaminergic wake neurons. EDS is relatively common in advanced Alzheimer's due to disruption of the sleep-wake rhythm and fragmentation of nocturnal sleep. This is compounded by the effect of sedative drugs. EDS may be predictive of later cognitive decline, and EDS complaints appear to predict later accumulation of amyloid markers on PET scans.

Epilepsy patients also frequently complain of EDS, commonly attributed to the use of antiepileptic drugs and to seizures (often subclinical at night and fragmenting sleep). The antiepileptic drugs most frequently involved are phenytoin, phenobarbital, benzodiazepines and gabapentin, while others, such as lamotrigine, are more neutral or even slightly wake-promoting (Fig. 3). Regardless of pharmacological treatment, sleep architecture is abnormal in many epileptic patients. This includes an increase in micro-arousals, arousals, and stage changes, a reduction in total sleep duration, slow wave sleep, REM sleep and sleep efficiency. Wake-promoting agents should be used with the utmost caution in these patients as they can increase the risk of seizure [167].

An accurate interview to look for symptoms associated with rEDS can lead to suspicion of neurological disorders: for example, if there are acute or chronic neurological symptoms such as headaches (migraines, facial vasculitis), sensory-motor deficit or cognitive disorders. The patient should then be referred to a neurologist. Brain imaging may be necessary. Management of these pathologies must be optimized when assessing rEDS in OSAHS, before considering a wake-promoting agent. A neurologist's opinion is essential, especially for neurodegenerative diseases [71]. Non-medical management is always a prerequisite, given the multi-factorial origin of EDS in these pathologies: reducing sedative treatments in the first instance, but sometimes also dopaminergic agonists (changing therapeutic class, testing prolonged-release medication, altering dosing times), educating patients and their families about the risk of accidents: avoiding driving, optimizing sleep hygiene (short, programmed naps are sometimes necessary).

Central disorders of hypersomnolence are rare but severe and disabling conditions affecting adolescents and young adults. They include narcolepsy type 1 (orexin/hypocretin deficiency syndrome) and type 2 [168], idiopathic hypersomnia [169], and Kleine-Levin syndrome [170]. Some *red flags* should raise suspicion of these disorders: young subjects (children, adolescents, young adults under the age of 40), rapid weight gain (a few months to one year), precocious puberty, severe EDS, dream activity during naps, sleep paralysis, sleep-related hallucinations, cataplexy, severe inertia (see details in Fig. 2). These disorders are rare, but they still take a very long time to diagnose in France (over 8 years), and this diagnosis must not be missed, as the consequences can be dramatic, particularly in terms of education and professional life [171]. Fig. S3 shows the care pathway in France, including assessment, diagnosis and standardized management of these conditions. These patients can be referred to expert centers, specialized in central disorders of hypersomnolence. A recent review also details the tools available to patients in France to help them overcome their disability, as well as the most appropriate professionals and structures to provide information [171].

Several comorbid sleep disorders could contribute to OSAHS rEDS. Restless legs syndrome is a sensory-motor disorder linked to dopamine deregulation, with central origin iron deficiency, in genetically predisposed subjects [172]. The diagnosis is clinical: patients describe unpleasant sensations in the lower limbs (restlessness), forcing them to move, relieved by movement, aggravated by immobility, and occurring in the evening and at night. EDS is present in a third of patients and is not very severe, but few studies have objectively investigated it, as this recent review points out [173]. It may be related to insomnia and the relative sleep deprivation it causes. The work-up should include measurement of plasma ferritin.

Neurological examination and electromyography (if performed) are normal. Sleep recording is not essential but can detect periodic limb movements during sleep (PLMS), which are associated in 80 % of cases. Daily management is reserved for severe forms and involves administration of low doses of dopaminergic agonists, alpha-2 delta-ligands and opioids, all of which are potentially sedative treatments (Fig. 3). Diagnosis and management of these disorders have been the subject of a SFRMS consensus [174–177]. Many patients with restless legs syndrome and/or periodic movements complain of fatigue, attention disorders, and EDS, but the direct links have not yet been studied in depth [7], and the attribution of these neurological disorders to EDS is still uncertain and debated [178,179].

Non-REM sleep parasomnias are frequent and often benign motor sleep disorders in children but can also be severe and persist into adulthood. They include sleepwalking, night terrors and confusional arousals [180]. Motor events can be complex and elaborate, and typically occur in the first part of the night, a few hours after falling asleep. Diagnosis is often easy on interview, but a PSG may be useful: during an episode, the EEG shows an aspect of dissociated wakefulness in slow wave sleep or characteristic grapho-elements called wakefulness hypersynchrony. Outside of episodes, slow wave sleep is fragmented, with fragmentation indexes it is possible to calculate. It has been shown that half of patients have EDS, especially in the morning [181]. This disorder should therefore be investigated during

the rEDS work-up, but treatment is not systematic and depends on the severity and frequency of the episodes and whether the patient is in danger.

Key points – Recommendations

- As part of the rEDS assessment of a patient with OSAHS it is recommended that comorbid neurological disorders be looked for and managed before considering prescribing a wake-promoting treatment.
- For patients with OSAHS and a neurodegenerative disease, it is imperative to seek the opinion of the neurologist before prescribing a wake-promoting agent.

Optimal management of other medical causes

Many medical causes: chronic inflammatory pathologies, cancers, metabolic disorders, endocrine disorders (obesity, hypothyroidism, diabetes, renal or hepatic failure), infections ("post-COVID-19" syndrome [182]), may be associated with EDS independent of OSAHS, possibly via low-grade inflammation. This is particularly true for obesity, which is closely associated with EDS even in the absence of OSAHS [183,184], and where an improvement in EDS is observed after weight loss, independent of AHI [185]. Obesity is associated with low-grade inflammation at the physio-pathological level, which may contribute to EDS due to an increase in cytokines and other inflammatory molecules released by adipose tissue [186]. It is also essential to rule out an obesity-hypoventilation syndrome insufficiently treated by the presence of daytime or nocturnal hypercapnia. This may be indicated by a high level of bicarbonates in venous blood and should lead to a pneumological assessment with at the least blood gases.

Management of these comorbidities should be considered and optimized. A minimum blood work-up is recommended (TSH, creatinine, ferritin, transaminases, blood count, bicarbonates and hs-CRP). Post-Covid-19 syndrome refers to symptoms persisting for more than 3 months following infection with SARS-CoV-2 ("long covid" refers to symptoms lasting longer than 1 month). No specific diagnostic criteria have yet been established for this recent syndrome, which only emerged in September 2020 [70]. There may be a phenotypic overlap between post-COVID-19 syndrome and chronic fatigue syndrome [187]. Patients with chronic pain also often have sleep fragmentation or insufficiently restorative sleep due to pain. This is visible on PSG with brief arousals preceded by K-complex (K-alpha figures) or alpha overload on stage N3 delta waves (alpha-delta figures) (Fig. S4). In this case treatment of nighttime pain must be optimized but treatments are often sedative and can sometime induce or aggravate EDS (Fig. 3). It has also been shown that the presence of nocturnal nasal obstruction, chronic rhinosinusitis such as nasal polyposis or allergic rhinitis, may be responsible for EDS [188] and poor CPAP compliance [189]. The patient may be offered medical and/or surgical treatment in addition to other measures if necessary. Some patients are exposed to repeated noise at night, fragmenting sleep, for example if they sleep near a busy road, an airport, next to a snoring spouse, or any other noisy environment. Repetitive noise can induce micro-arousals which are not perceived but which add up to a feeling of non-recuperative sleep [190]. Avoidance of noise or use of hearing protection can eliminate nocturnal noise related EDS.

Key points – Recommendations

- As part of the rEDS assessment of a patient with OSAHS it is recommended that comorbid medical disorders be looked for and managed before considering prescribing a wake-promoting treatment.
- A minimum blood screening test should be conducted: TSH, creatine, transaminases, ferritin, blood count and hs-CRP.
- In the case of obesity:
  - Obesity is not a contraindication to prescribing a wake-promoting treatment in a long-term CPAP treated patient with OSAHS. However, it is recommended to consider first all the possibilities to manage this comorbidity with the patient: hygienic and dietary measures or even bariatric surgery.
  - It is then essential, during follow-up, to regularly re-examine the treatment options with the patient, even if he initially refused the options.
- In the case of chronic nasal obstruction. It is recommended to assess and manage the presence of nasal obstruction and a change in sleep quality in relation to rhinological symptoms that may be responsible for EDS.

Non-pharmacological management of sleepiness and therapeutic education

Even in the absence of a sleep debt, behavioral sleep hygiene measures (adopting regular sleep schedules, avoiding sleep deprivation situations; scheduling anticipated naps, preferring short naps < 15–20 min) can reduce EDS and should always be considered whatever the cause of EDS. Regular physical exercise, exposure to daylight, especially in the morning, eating regular meals that contain less fast sugars, and drinking tea and coffee are all part of non-drug therapies for EDS. Providing therapeutic education to patients about the condition and treatment is an essential and integral part of quality care. The deleterious effect of several treatments on alertness, sedative treatments in particular (Fig. 3) must be explained to patients to limit iatrogenicity and self-medicating. In a patient with long-term CPAP treated OSAHS prescribing a wake-promoting agent and a sedative effect treatment at the same time would be the exception rather than the rule and should only occur after first discussing all the options with the patient: stopping sedative treatment, changing therapeutic class, reducing dosage, altering dosing times (evening rather than afternoon or morning). The authors of this consensus consider that a collegial discussion is necessary before introducing a wake-promoting agent in this context.

6. Treating sleepiness with wake-promoting medication

After a comprehensive assessment, and if sleepiness is constant, disabling and unresponsive to behavioral measures (extending sleep time, rest, naps), (Summary Fig. 1) prescription of a wake-promoting agent may be considered. Fig. S5 lists the market authorizations for the two treatments available in France: solriamfetol and pitolisant, and the conditions under which they are reimbursed by the social security system. These two compounds were initially tested and received marketing authorization for narcolepsy. Pitolisant is marketed under the name Wakix® in this indication (but is the same compound). A summary of clinical trials of the efficacy and tolerability of these two compounds in OSAHS patients with rEDS is provided in Table S2 [110,191–194] ("main" studies only).

The exclusion criteria are listed in detail to clarify which populations have been included in these clinical trials. There are differences between the clinical trials (selected populations), the market authorizations and the reimbursement criteria. The safety and effectiveness of these treatments in this indication in children and adolescents (<18 years old) have not been established. The clinical trials were carried out in patients who had not (either currently or in the past) used or been substance dependent, and there is very little data in populations with psychiatric disorders, which therefore require future tolerance studies. It is still possible in some cases to prescribe both a

wake-promoting agent and a psychiatric treatment, but this should only be considered after specialist advice from a psychiatrist, and as a part of regular follow-up of psychiatric treatment. The summaries of product characteristics (SmPCs) for solriamfetol and pitolisant are given below.

6.1. Solriamfetol, Sunosi®

The mechanism of action of this wake-promoting agent is related to inhibiting the reuptake of dopamine and noradrenaline [195,196].

Solriamfetol binds to dopamine and noradrenaline transporters but only interferes slightly with serotonin transporters. It inhibits presynaptic reuptake of dopamine and noradrenaline by these transporters, increasing their levels in the synaptic cleft. However, solriamfetol does not “force” their release from the presynaptic neuron (unless used in supramaximal doses). This explains the absence of rebound hypersomnia on solriamfetol withdrawal in rodents [197]. Compared to modafinil (whose mode of action uses the dopamine transporter) solriamfetol has an additional faciliatory action on noradrenergic transmission. It has no action on histaminergic or orexinergic transmission. It has little addiction potential. Solriamfetol has cardiovascular effects (tachycardia, possible hypertension due to sympathetic hypertonia). This effect is dose-dependent and remains moderate at therapeutic doses.

6.1.1. In clinical practice

The recommended initial dose is 37.5 mg/day in the morning, taken orally, with or without food. 75 mg and 150 mg divisible tablets are available.

Depending on the clinical response, the dosage may be increased by doubling the dose at intervals of at least 3 days, with a maximum daily dose of 150 mg/day. It does not require a "secure" prescription in France, but the initial prescription is hospital based. This can only be issued by specialists in neurology, pneumology or those that have completed specific post graduate sleep training (the *Formation Spécialisée Transversale Sommeil*), and physicians practicing in sleep centers (see SmPC SOLRIAMFETOL and the opinion of the commission de transparence). Only these practitioners are authorized to continue prescribing the product. The main contraindications are unstable cardiovascular comorbidities: history of myocardial infarction over the previous year, unstable angina, uncontrolled hypertension, serious arrhythmias and other significant cardiac conditions, and concomitant treatment with monoamine oxidase inhibitors (MAOI), or within 14 days after the end of such treatment. If there is any doubt about the stability of cardiovascular comorbidities, and depending on clinical evaluation, the opinion of a cardiologist may be sought, to verify the stability of cardiovascular disorders, ensure that their management is optimal, and discuss the benefit-risk ratio of the prescription.

The most frequently reported adverse effects are headache, nausea and loss of appetite, leading to weight loss of >5 % in a subpopulation of treated patients [198].

6.1.2. Specific populations

Data available in elderly patients (>65 yo) are limited, and the use of lower doses and close monitoring should be considered in this population. Solriamfetol is eliminated mainly by the kidneys and a dose adjustment may be necessary. It has not been evaluated in patients with psychotic or bipolar disorder. Particular attention should be paid to these patients, due to psychiatric side effects that may exacerbate psychiatric disorders: for example, induced manic episodes. Treated patients must be closely monitored to detect side effects like anxiety, insomnia and irritability. These adverse effects were frequently observed when treatment is initiated but tended to resolve with continued therapy. In the event of persistence or aggravation, dose reduction or discontinuation of treatment should be considered.

Efficient contraception is recommended in women of childbearing age since, according to current guidelines, solriamfetol during pregnancy is not recommended. Solriamfetol has no pharmacokinetic interaction with oral contraceptives.

Patients with significant (but stable, otherwise considered a contraindication) cardiovascular comorbidities require close monitoring, especially of blood pressure, and a cardiologist’s opinion sought to discuss the benefit-risk balance of the prescription.

6.1.3. Monitoring

Blood pressure (BP) and heart rate (HR) should be measured before treatment initiation, and regularly thereafter, especially after a dose increase, ideally by self-measurement (HAS recommendation) or with ambulatory BP monitoring (ABPM). Solriamfetol appears to increase systolic BP and HR in a dose-dependent way (particularly above 150 mg/day, which explains why the 300 mg/day does not have market authorization). The increase in BP exists during the day but, due to pharmacokinetic characteristics, does not modify the characteristics of nighttime BP. The benefit-risk balance must be carefully assessed at initiation and during follow-up. Pre-existing hypertension should be stabilized prior to initiating treatment, and patients with a higher risk of major cardiovascular events (e.g. pre-existing hypertension, cardiovascular or cerebrovascular disease, elderly patients) should be treated with caution. Continuation of solriamfetol should be assessed at regular intervals. If a patient presents with increases in BP or HR that cannot be controlled by dose reduction or other appropriate medical intervention, discontinuation of solriamfetol should be considered. The need for continued treatment and the appropriate dose should be reassessed periodically during long-term therapy. This is even more important since OSAHS patients often present with multiple cardiovascular risk factors: hypertension, diabetes, dyslipidemia; overweight.

Solriamfetol is contraindicated in cases of severe cardiac disease, including pulmonary arterial hypertension (PAH) and other causes of pulmonary hypertension (particularly those associated with left-sided heart failure, chronic respiratory disease or chronic thromboembolic disease), as well as severe valvular disease. Patients with cardiovascular comorbidities should undergo regular monitoring, particularly of BP, by a cardiologist to confirm the appropriate benefit-risk balance of the prescription.

6.1.4. Specific situation: pulmonary arterial hypertension (PAH)

Potential solriamfetol related complications of PAH or valvulopathy cannot yet be formally ruled out, even if this risk has not been proven to current knowledge, in its indications and at the usual doses. This risk could, theoretically, exist for all other wake-promoting agents. If there is a diagnostic doubt, it is mandatory to notify the relevant Pharmacovigilance Centre.

It is therefore important to inform patients that, in the event of dyspnea, they should consult as soon as possible to limit the delay in diagnosing these potentially severe complications. Echocardiography, a screening test for these two complications, should be performed by a physician familiar with these diseases, based on the onset of symptoms (dyspnea, malaise, syncope, heart murmur, clinical signs of heart failure). A chest X-ray and dose of NT-proBNP or BNP can complete the screening workup. For an abnormal examination that raises suspicion of PAH or valvulopathy, the patient should be referred to a specialized center. PAH is a rare disease, and in France, there is a dedicated Pulmonary Hypertension network (PulmoTension) including a reference center (pneumology department, Hôpital Bicêtre, AP-HP, Paris-Saclay University) and competence centers spread throughout the country. A PAH diagnosis can be confirmed or disconfirmed by right-heart catheterization performed in one of these specialized centers. If valvulopathy is suspected, a specialist opinion from a cardiology center with multidisciplinary expertise in drug-induced valvulopathy is recommended. The sleep specialist must be especially

attentive to known risk factors for PAH in these patients: connective tissue diseases, portal hypertension, HIV infection, congenital heart disease or genetic predisposition to PAH.

In compliant patients, a wake-promoting pharmacological treatment may in theory reduce the motivation to use CPAP, and this has been reported with modafinil. To date, short and long-term data for solriamfetol show no reduction in compliance [110,199]. The study of the risk of addiction to solriamfetol demonstrated a potential inferior to, or comparable with, the stimulant phentermine [200]. It is included on the list of addictive drugs in the United States (FDA) with an overall potential equivalent to modafinil (lower than methylphenidate).

6.2. Pitolisant, Ozawade®

The mechanism of action of this treatment is unique: it is an antagonist/reverse agonist of the histamine H3 receptor. By blocking these presynaptic receptors, it strengthens histaminergic transmission. It also indirectly modulates other neurotransmitter systems, increasing the release of acetylcholine, noradrenalin and dopamine. Pitolisant has no vasopressor effect in animals or humans [193,194,196].

6.2.1. In clinical practice

This treatment should be used at the lowest effective dose, based on clinical response and tolerability. It should be taken in the morning, in one oral dose, during breakfast and before midday. The indication is for moderate to severe OSAHS, not mild OSAHS. Prescription does not require a "special" form in France, but the initial prescription is hospital-based as is each subsequent, annual prescription of the product. It can only be issued by specialists in neurology, pneumology or those that have completed specific post graduate sleep training (the *Formation Spécialisée Transversale Sommeil*), and physicians practicing in sleep centers.

Within one calendar year of prescription, a physician may renew the prescription without restriction, but the patient must return annually. Treatment must be initiated by a “physician specializing in OSAHS and cardiovascular risks” (see PITOLISANT and Transparency Commission Opinion). OSAHS must be evaluated annually, at least during a consultation. Two doses exist: 4.5 mg and 18 mg tablets. The optimal therapeutic dose should be achieved step by step, not exceeding 18 mg/day (lower doses than those used in narcolepsy [201]). The first week an initial dose of 4.5 mg/day is proposed, then in the second week the dose can be increased to 9 mg/day, and in the third week can be increased to 18 mg/day or decreased to 4.5 mg/day. The dose can then be reduced (to 4.5 mg/day) at any time or increased (up to 18 mg/day) based on the physician’s assessment and patient’s response. The only contraindication is severe hepatic impairment. The most frequently reported adverse effects are headache and insomnia (manifesting above all as more frequent awakening at night). Very rare cases of depressive episodes (3 %) and manic episodes have been reported with pitolisant.

6.2.2. Special populations

Available data in elderly patients (>65 years old) are limited, and the use of lower doses and close monitoring must be considered in this population. Pitolisant should be used with caution in patients with a history of psychiatric disorders like severe anxiety or severe depressive disorder with risk of suicide. Efficient contraception is recommended in women of childbearing age, as current guidelines do not recommend pitolisant administration during pregnancy. There is a “theoretical” pharmacokinetic interaction with oral contraceptives (based on in vitro data: potential induction effect of cytochrome CYP3A4, thus potential reduction in the efficacy of hormonal contraception) [202]; an alternative mode of contraception may therefore be proposed. In practice however there are currently no data in women demonstrating a reduction in the efficacy of contraception with pitolisant.

6.2.3. Monitoring

Tricyclic or tetracyclic antidepressants may modify the effectiveness of pitolisant due to their histamine H1 receptor antagonist action and may negate the effect of endogenous histamine released in the brain under the effect of the pitolisant. An alternative must be used. Antihistamines (H1-receptor antagonists) that cross the blood-brain barrier may alter the effectiveness of pitolisant and an alternative should be used. Combination with drugs that prolong the QT interval or with a risk repolarization disorders (haloperidol, risperidone, erythromycin, clarithromycin, etc.) may be used, but only under close supervision. No special monitoring of BP or HR is required for patients in general.

However, it is reasonable to suggest self-monitoring BP and HR to at-risk subjects (known hypertension, high cardiovascular risk, borderline BP at initiation). Pitolisant may prolong the QT interval, but current data show that it has no impact on cardiovascular safety in OSAHS patients whether treated [193] or not treated with CPAP [194], no change in BP or HR was seen. The benefit-risk balance, the need to continue pitolisant therapy, and the dose should be reassessed at regular intervals. The aim is to monitor compliance and above all encourage the patient to continue OSAHS treatment, and to maintain good sleep hygiene. There are currently no data on the impact that rEDS prescribed pitolisant might have on CPAP compliance (but no excess cardiovascular risk is expected in the non-adherent group, according to published data [194]).

The FDA commissioned study of the addiction risk of pitolisant demonstrated an addictive potential comparable to placebo [203]. It therefore does not figure on the list of addictive drugs in the United States (FDA website).

6.2.4. Other wake-promoting treatments

Other wake-promoting treatments such as modafinil, methylphenidate and amphetamines are sometimes used off-label to treat OSAHS rEDS. Modafinil showed a beneficial effect on rEDS in large, double-blind, placebo-controlled trials and was therefore granted the rEDS indication in 2004, noting that a reduction in CPAP compliance had been observed in the CPAP and modafinil combination. It lost the indication in France in 2011 as part of a global re-evaluation of modafinil in various indications following reports of psychiatric adverse effects, one case of Stevens-Johnson in a child, and mild modifications in BP. In the absence of available randomized controlled trials, the amount of evidence is insufficient to assess the efficacy and tolerability of methylphenidate and amphetamines in this indication. The side effects of these drugs, and their potential for abuse and addiction, limit their use. At peripheral level in the short term, the sympathomimetic effect of amphetamines leads to cardiac stimulation, with tachycardia associated with palpitations, HTA and rhythm disorders. In the long term, pharmacovigilance data collected over 30 years following the use of some amphetamines as anorectics, fenfluramine in particular (PONDERAL®, withdrawn from the French market in 1997), dexfenfluramine (ISOMERIDE®, withdrawn from the French market in 1997) and benfluorex (MEDIATOR®, withdrawn from the French market in 2009), have confirmed a risk of PAH and irreversible valvulopathy associated with amphetamines [204–208]. The authors of this paper consider that these treatments are not recommended in OSAHS rEDS.

Key points - Recommendations

BEFORE prescribing a wake-promoting treatment to a patient with treated OSAHS:

- It is recommended to: (1) conduct an initial diagnostic procedure to rule out sleep insufficiency, a sleep, wakefulness or circadian rhythm disorder, the use of substances or sedative medication, or

a neurological, psychiatric, ENT or medical disorder responsible for EDS, and (2) check the effectiveness of and compliance with CPAP (at least 6 h/night, most nights, for at least 6 months).
- It is recommended that measures be taken to improve sleep hygiene and reduce the EDS: scheduled naps, exposure to daylight in the mornings, regular physical exercise, avoidance of rich, fatty and sugary foods, and drinking tea or coffee.
- It is recommended that a sleep specialist complete the assessment (PSG, MSLT, etc.) in the following situations:
  - When the patient is insufficiently CPAP compliant, despite their and the physician's best efforts to optimize compliance.
  - When there are potential causes of EDS other than OSAHS, especially multiple causes (e.g. depressive symptoms, chronic sleep debt, obesity).
  - When there are *red flags* (Fig. 2) pointing to the presence of hypersomnolence of central origin.
  - When there are comorbid disorders, especially other clinically significant sleep disorders: restless legs syndrome, insomnia, nocturnal nasal obstruction, etc.
- It is recommended, in patients with psychiatric comorbidities, that the opinion of a psychiatrist verify the stability of the psychiatric disorders to ensure that they are optimally managed, and to discuss the benefit-risk balance of the prescription.
- It is recommended, in case of doubt about the stability of cardiovascular comorbidities, especially before prescribing solriamfetol, that a cardiologist checks the stability of the cardiovascular disorders to ensure that they are optimally managed, and to discuss the benefit-risk balance of the prescription.
- It is not recommended to prescribe a wake-promoting treatment and a treatment with a sedative effect at the same time in most cases. Co-prescribing is possible in exceptional situations, and only after all options have been discussed with the patient beforehand: stopping the sedative treatment, changing therapeutic class, reducing dosage, changing the times at which medication is taken. In these cases, it is essential to have a collegial discussion to validate the prescription.

Choice of the wake-promoting treatment

- The initial prescription of pitolisant and solriamfetol is made at hospital, as is the annual renewal. Only specialists in pneumology, neurology, or MD trained in the *Formation Spécialisée Transversale Sommeil* (FST) and practicing in sleep centers can prescribe these treatments.
- It is recommended that BP and HR be measured when treatment is initiated.
- The choice of 1st or 2nd line treatment is based on clinical judgement:
  - It is suggested that pitolisant should be prescribed as 1st line treatment if there are cardiovascular comorbidities or risk factors for PAH or psychiatric conditions.
  - If the 1st line wake-promoting treatment (pitolisant or solriamfetol) is ineffective or poorly tolerated the 2nd line treatment may be offered, in the absence of contraindications.
- It is recommended not to prescribe wake-promoting treatments without market authorization (MA) as 1st or 2nd line option, such as modafinil, methylphenidate, or amphetamines.

AFTER prescribing a wake-promoting treatment to a patient with treated OSAHS

- It is recommended to reassess the need to continue the treatment, and monitoring at regular intervals. The authors of this consensus suggest follow-up at 3 months after introduction, then between 6 and 12 months, an annual follow-up, for example, and based on clinical judgement. It is recommended that this follow-up include:
  - Subjective assessment of treatment effectiveness (interview, scales).
  - Assessment of tolerance and side effects.
  - Evaluation of psychiatric symptoms, particularly anxiety and depression.
  - Measurement of HR and BP:
    - ☐ For solriamfetol: it is recommended to regularly monitor HR and BP, especially after a dose increase, ideally through self-measurement of BP or ABPM, in all patients.
    - ☐ For pitolisant: it is recommended that HR and BP be monitored regularly, by self-measurement of BP, in at-risk patients (known hypertension, high cardiovascular risk, borderline BP at initiation).
  - Verification of compliance and the effectiveness of the primary treatment of OSAHS [(4)].
  - Look for and reassess other causes of EDS that could be treated, even if they were not initially present.
- Cardiac ultrasound is recommended if symptoms appear suggesting PAH or valvular disease (dyspnea, malaise, syncope, heart murmur, heart failure) in a patient being treated with a wake-promoting agent for rEDS. The patient should be referred to a specialist center in the event of an abnormal result suggesting PAH or valvular disease.
- If psychiatric symptoms appear, it is recommended to request a psychiatric evaluation.
- It is imperative that drivers undergo MWT (at least 1 month after treatment initiation) to confirm that wakefulness has been restored and to renew the patient's fitness to drive motor vehicles (for timelines see *Medicolegal consequences, driving* Arrêté 28th March 2022).

[(4)] In some situations, OSAHS needs to be reassessed/re-indexed during follow-up, for example after weight loss, after bariatric surgery, after surgical management of OSAHS, or when comorbidities appear (OSAHS can be reversed but can also worsen or change phenotype).

Indication of a wake-promoting treatment in sleepy patients with OSAHS refusing or nonadherent to CPAP

The indication of a wake-promoting pharmacological treatment in sleepy patients with OSAHS refusing or nonadherent to CPAP (or for whom it is contraindicated) is a complex situation that raises many questions and is the subject of debate within the scientific community and our consensus group [194,209]. Some of us are concerned that this clinical attitude is tantamount to "flogging a dead horse" and note that it has not yet been demonstrated that giving pitolisant to a sleepy patient with untreated OSAHS would protect them against the risk of an accident when driving or operating machinery. If, in the opinion of the clinician, sleepiness poses such a risk to the patient, it would seem clinically logical to perform a MWT before and after prescribing a wake-promoting agent. Pitolisant (Ozawade®) received MA for patients who have tried CPAP, are intolerant of it and have tried MAD (or have contraindications to it). This follows a single randomized controlled trial which demonstrated efficacy on sleepiness in these patients, who had an average ESS score of 15 at the start of the trial, with no adverse cardiovascular effects. It should be noted that the placebo effect was significant (- 3.6 points on the ESS score) which clearly illustrates the variability of the ESS score over time. The effectiveness of pitolisant (like solriamfetol) to improve subjective and objective sleepiness was the same in patients treated with CPAP or not.

In any case, the authors of these guidelines insist that a wake-promoting agent should never be considered a first line treatment for OSAHS.

For all patients with OSAHS efforts must be made to maximize compliance and optimize the primary treatment of OSAHS: therapeutic education, weight reduction, and therapeutic alternatives. These include MAD, positional therapy, ENT surgery if the therapeutic indication is confirmed (on awake examination in cases of Friedman grade $^{3}/_{4}$ tonsillar hypertrophy without major retro-basilingual obstruction [Mallampati 1/2 score], or when performing induced sleep endoscopy to contraindicate surgery in the case of obstructive phenotype, prognostic of non-response to surgery) (see French recommendations 2022 SPLF/SFORL/SFAR/AFSORL [133]). The therapeutic option of hypoglossal nerve stimulation in the event of CPAP and MAD failure in symptomatic patients with moderate to severe OSAHS (AHI between 15 and 50/h) may be proposed, in the absence of a concentric collapse of the soft palate and if BMI <32 kg/m^2 (favorable opinion from HAS March 2022, improvement in expected service [ASA] IV).

If this approach is unsuccessful despite the patient's best efforts (and the physician's efforts to convince them), then the decision to introduce pharmacological treatment is based on clinical judgement, obviously after having investigated all causes other than the OSAHS that could potentially explain the rEDS (see previous sections Behavioral Management of Sleepiness: sleep debt to non-pharmacological management, therapeutic education). The prescription may be considered when EDS is especially bothersome or dangerous, but also when the patient asks for treatment. However, it is strongly recommended that a sleep specialist be consulted beforehand as prescription conditions are restricted (see below). Prescribing a drug of this type requires regular assessment of the situation and annual monitoring of the OSAHS (at least during a consultation or even reindexing with a RP or PSG) and does not mean that a first line treatment for OSAHS should not be tried again. Note that there are no data on other treatments for OSAHS (MAD or surgery in particular) that might have failed for the patient, since the study covered patients with failed CPAP.

Key points – Recommendations

BEFORE considering prescribing pitolisant in a patient with failed primary treatments for OSAHS:

- It is recommended that an initial diagnostic be conducted to rule out sleep insufficiency, a sleep, wakefulness or circadian rhythm disorder, the use of substances or sedative medication, or a neurological, psychiatric or medical disorder responsible for EDS (Summary Fig. 1);
- It is recommended that measures be taken to improve sleep hygiene and reduce the EDS: scheduled naps, exposure to daylight in the mornings, regular physical exercise, avoidance of rich, fatty and sugary foods, and drinking tea or coffee;
- It is recommended to seek the opinion of a sleep specialist before introducing this treatment, to complete the assessment and consider all options for the management of OSAHS. It is especially recommended that an ENT assessment be conducted to clarify the anatomical phenotype of the OSAHS.

AFTER prescription of pitolisant in a patient with failed primary treatment for OSAHS:

- It is recommended reevaluating the need to continue the treatment, and monitoring at regular intervals. The authors of this consensus suggest follow-up at 3 months after introduction, between 6 and 12 months then an annual follow-up for example, based on clinical judgement;
- It is recommended that this follow-up include:
  - Subjective assessment of the effectiveness of the treatment (interview, self-assessment questionnaires),
  - Assessment of tolerance, side effects (especially insomnia, headaches and psychiatric symptoms, anxiety and depression),
  - Clinical examination to monitor cardiovascular risk factors: weight, HR and BP. It is recommended to control BP by self-measure in at-risk patients (known hypertension, high cardiovascular risk, borderline BP numbers on initiation)
  - On each visit, discuss with the patient resuming primary treatment for OSAHS, or an alternative if the treatment has already been abandoned,
  - Look for and reassess other causes of EDS that could be treated, even if they were not initially present,
  - Annual reassessment of the OSAHS [(6)]
- In the appearance of psychiatric symptoms in a patient treated with pitolisant it is recommended that a psychiatric evaluation be requested;
- It is imperative that drivers undergo MWT (at least 1 month after treatment initiation) to confirm that wakefulness has been restored and to renew the ability to drive motor vehicles (for timelines see *Medicolegal consequences, driving* Arrêté 28th March 2022).

[(6)] In this case it is recommended that a specialist consultation for OSAHS be carried out at least once a year and suggested that a ventilatory polygraphy or polysomnography be performed.

7. Medicolegal consequences, driving

Sleepiness at the wheel is a frequent cause of road accidents, along with alcohol consumption and speeding, and is involved in around 30 % of fatal motorway accidents. The presence of incapacitating sleepiness while driving (the need to stop driving during a planned journey, or uncontrolled lane crossings over the past year) multiplies the risk of accident by two [210]. CPAP treatment significantly reduces the risk of accident [211]. Two recent studies demonstrated an objective improvement in driving performance on solriamfetol in a population of patients with OSAHS and rEDS and another of patients with narcolepsy [212,213].

The ministerial order of 18th December 2015 updated 28th March 2022: Arrêté 28th March 2022 lists medical conditions incompatible with obtaining or retaining a driving license or receiving an unlimited validity license. EDS, regardless of cause, is on the list. Physicians must inform patients with OSAHS with rEDS of the risks inherent in driving and of the need to contact a qualified physician, on their own initiative, to validate their driver's license. Physicians are bound by professional secrecy and cannot therefore report at-risk drivers (however the patient's family and friends can report them to the prefecture) but they must be able to provide proof that they have informed the patient and done everything in their power to persuade the individual to declare the condition. Note that the assessment of fitness to drive takes place at least one month after a specialist's assessment of therapeutic effectiveness on the EDS. There is incompatibility if EDS persists despite therapeutic management.

At present, the law requires an annual MWT for drivers in the heavy group (group 2, taxi drivers, chauffeur driven vehicles, ambulances, school buses, vehicles used for the public transport of people; driving two or three-wheeled motorized vehicles for the paid transport of people, driving lessons). The qualified physician or medical commission will consider the MWT to assess fitness to drive, authorized on a temporary basis, for 1 year (in the absence of a change in the symptomology and/or treatment, and/or medical advice to the contrary). The previous 2015 Order made no requirement of MWT for the light group (group 1, driving license for non-professionals). MWT is now mandatory every 3 years for this group. The specialists treating sleepiness (and also the qualified physician and the prefectural medical commission) have to decide which investigations to conduct, based on their clinical assessment. They may request a

MWT if necessary, before the legal 3-year deadline. Driving is authorized temporarily, for 3 years, if there is no change in the symptoms and/or treatment, and/or medical opinion to the contrary).

For professional drivers, severe rEDS means that they must consult their occupational physician as soon as possible. For the sleep specialist, this involves either referring these people to an occupational physician, or responding to the occupational physician if the patient is referred by the latter. The occupational physician assesses fitness for work and the additional risks associated with working and driving conditions. Physicians are bound by professional secrecy and may not report at-risk drivers to the occupational physician unless the latter initiates the request for a medical opinion about the rEDS. Proof must be provided, by any means, that the patient has been informed and that they have done everything to persuade them to declare the rEDS. It is the occupational physician that decides on job fitness with rEDS, and the sleep physician is not obliged to prescribe sick leave for rEDS.

The authors of this consensus, on behalf of the medical community of sleep specialists, would like to stress that the new law, in its current wording, is difficult to apply to all patients with sleepiness at the wheel. Sleepiness in any situation is a very common condition in the general population: 27.8 % complain of EDS, 4.7 % with the addition of frequency criteria (>2 bouts of sleep or inability to remain alert per day, >3 times per week for >3 months), and 1.5 % after eliminating the most common causes (such as sleep deprivation) [214]. The availability of sleep centers in France approved to conduct wakefulness tests, is currently not enough to meet this demand for non-professional drivers: several million non-professional drivers are potentially concerned. The authors of the consensus therefore consider that the obligation to perform these tests should be limited, as specified in the previous version of the Order, to professional drivers, especially when they need to drive for long periods and/or at night.

Key points – Recommendations

- In a patient with CPAP treated OSAHS current legislation requires objective measurement of sleepiness by MWT every one to three years, depending on the type of driving license, to ensure there is no risk (see Arrêté 28th March 2022).
- It is recommended, in addition to these objective evaluations, that the risk of EDS related driving accidents should be systematically assessed by asking the patient about the occurrence of disabling sleepiness at the wheel, causing lane crossing or the need to stop. A question can be asked [(1)], or a specific scale used (the BOSS scale) [88], validated markers of accident risk.

[(1)] "Over the past year have you experienced at least one episode of severe sleepiness at the wheel making driving difficult or forcing you to stop?".

8. Conclusion and perspectives

EDS is a common complaint in the general population; most frequently caused by mood disorders and chronic sleep debt. In a patient with OSAHS, additional mechanisms are often interrelated to explain the EDS. The socio-professional and public health consequences are significant: lower quality of life, risk of accidents, especially when driving, at work, at home, with medicolegal implications. When dealing with a complaint of rEDS in a patient with treated OSASH, the first question a physician should ask is: "is the OSAHS being treated correctly?" Before initiating medical management, the efficacy of the treatment must be verified, the existence of OSAHS treatment side-effects impacting sleep quality must be assessed, and all other causes of rEDS must be investigated and treated if necessary (Summary Fig. 1). When there is an indication for a wake-promoting agent close follow-up is recommended and cardiovascular risk factors must be controlled well (Summary Fig. 1).

The indication for a wake-promoting treatment is only for patients with obstructive SAS, in the absence of any published data to date on rEDS in central, mixed, combined or emergent SAS (with a certainly higher cardiovascular risk). There are also no studies available on EDS in patients with mild OSAHS, or with sleep-disordered breathing such as high upper airway resistance syndrome [60,122]. In this case it is uncertain that EDS can be attributed to OSAHS, and further studies are needed to better understand these conditions.

It should be emphasized that to date there are no studies available directly comparing solriamfetol and pitolisant, on efficacy and tolerability, in the short and long term. Only indirect comparisons between the two compounds can be drawn, using data from randomized trials conducted in different populations, with inclusion and exclusion criteria that are similar but different, and evaluation criteria that are also different.

The clinician must therefore retain their clinical and critical sense in this situation because although market authorization for these agents means that thousands of patients in France can potentially be treated, it is nevertheless necessary to call on the multidisciplinary skills of sleep medicine to precisely define the indications, plan an exhaustive preliminary assessment, sometimes request specialist opinion, assess the benefit-risk balance of the treatment and monitor these patients very closely.

Research agenda

- ☐ Explore the pathophysiological mechanisms underlying rEDS in OSAHS as well as EDS in OSAHS.
- ☐ More specifically phenotype sleepiness in patients with OSAHS with the use of self-assessment questionnaires developed specifically for this patient population [215], and objective tests of sleepiness and wakefulness, adapted to and standardized for these populations.
- ☐ Identify the factors associated with a better response to wake-promoting treatment (clinical, phenotypic and pharmacogenetic determinants), to identify "non-responders" and "best-responders" among patients with OSAHS and rEDS.
- ☐ Identify the factors associated with objective sleepiness in these populations and understand the responsibility of OSAHS in EDS (links to AHI, with the desaturations index, impact of upper airways high resistance syndrome).
- ☐ Study the effects of wake-promoting treatments on neuroimaging changes observed in patients with OSAHS and rEDS.
- ☐ Study the impact of wake-promoting treatments on sleep macro- and microarchitecture and respiratory events in patients with OSAHS and rEDS.
- ☐ Study the impact of wake promoting treatments on cognitive performance in patients with OSAHS.
- ☐ Study the long-term effect of wake-promoting treatment on CPAP compliance in patients with treated OSAHS.
- ☐ Study the long-term effects of wake-promoting treatment on lifestyle, habits, behavioral changes, physical activity and weight.
- ☐ Conduct direct comparative studies of the efficacy and tolerability (especially cardiovascular) of wake-promoting agents available with the rEDS indication in patients with OSAHS.
- ☐ Study the efficacy and tolerability of other drug treatments in the rEDS indication in patients with CPAP treated OSAHS (e.g. orexin 2 receptor agonists, phase 1b study recently published [216]).
- ☐ Create prospective registries ("real-life" population studies) to evaluate the long-term benefits, safety and tolerability of

wake-promoting agents, including morbi-mortality in patients with OSAHS and cardiovascular comorbidities.
- ☐ Study the effect of a wake-promoting treatment for rEDS in OSAHS patients on psychiatric symptoms and psychiatric comorbidities (not contraindicating the introduction of such a treatment).

Declaration of competing interest

Pr Andrejak has been a speaker at symposiums for Moderna, Chiesi, AstraZeneca et Insmed, unrelated to this subject. Pr Arnulf was a paid consultant for Idorsia Pharma in 2020 and unpaid for Takeda Pharma in 2022, unrelated to this subject. Dr Baillieul has been paid for work for Jazz Pharmaceuticals; clinical study investigator for Bioprojet; received support from Agiradom, Vitalaire and Bioprojet for participation in a congress. Dr Barateau was a consultant for Bioprojet, Takeda, Idorsia, and Jazz Pharmaceuticals between 2020 and 2022, and a speaker for Bioprojet, Jazz Pharmaceuticals and Idorsia. Dr Bequignon has been a consultant for Air Liquide Santé, GSK, Sanofi, paid talks for Bioprojet, Inspire, GSK, Sanofi, Amplifon. Pr Boutouyrie was a consultant for Bioprojet and Jazz-pharmaceutics in 2021 and 2022, related to this subject. Pr Dauvilliers has been consultant and speaker and has been invited to conferences by UCB Pharma, Jazz, Theranexus, Idorsia, Takeda, Avadel and Bioprojet. Pr Gagnadoux has worked as consultant for Air Liquide Santé, Asten santé, Bioprojet, Inspire, Sefam, Resmed; and as a paid speaker for Bioprojet, Cidelec, Inspire, Jazz Pharmaceuticals, Philips Respironics. Pr Geoffroy has been paid speaker for Biocodex, Bioprojet, Idorsia, Janssen-Cilag, Jazz pharmaceuticals, Lundbeck, MySom- meil, Withings; received fees as expert for Apneal, Biocodex, Dayvia, Idorsia, Janssen-Cilag, Jazz pharmaceuti- cals, Myndblue, Posos, ResilEyes, Withings; and is a member of the advisory boards of: Apneal, Idorsia, Mindblue, Mysommeil. Dr Jaffuel has been involved in clinical trials, scientific work, consulting, conferences, symposiums and other activities over the past 5 years for the following companies and organizations: ALK, AstraZeneca, Bohringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Sanofi; en rapport avec l'article, Adene, Bastide, Bioprojet, Jazz, Löwenstein, LVL, Nomics, Philips Respironics, Resmed, Sefam, Tali. Pr Micoulaud-Franchi has been a consultant for Gilead, Eisai et Bioprojet. Pr Monaca has been speaker for UCB Pharma, Jazz; consultant for Resmed, investigator for Jazz, Bioprojet, Theranexus. Pr Montani and Dr report no conflicts of interest. Dr Patout: research project funding: Fisher & Paykel, Resmed, Asten Santé - Consultant: Resmed, Philips Respironics, Asten Santé, GSK - Paid talks: Philips Respironics, Resmed, Elivie, SOS O2, Chiesi, Asten Santé, Air Liquide Medical Système, Antadir, Jazz Pharmaceutical, Lowenstein - Actions: Kernel Biomedical - Conference support: Asten Santé. Pr Pépin has received research funding from: Air Liquide Foundation, Agiradom, AstraZeneca, Fisher and Paykel, Mutualia, Philips, Resmed and Vitalaire; et a été consultant pour Agiradom, AstraZeneca, Boehringer Ingelheim, Jazz pharmaceutical, Night Balance, Philips, Resmed et Sefam. Pr Philip reports that he has been a consultant for Jazz Phar maceuticals and Bioprojet. Pr Tamisier has received payment for scientific communication from Resmed, Philips, Elivie and Agiradom, support for participating in a congress for Laboratoires Agiradom. RT received financing for research from Fondations Resmed APMC, Resmed, Philips, and Vitalaire, took part in scientific committees for Respicardia, Sorin et Jazz Pharmaceutical, Inspire and Resmed. Pr Trzepizur was invited to scientific congress by Asten and gave a paid talk for AstraZeneca.

Acknowledgement

Medical writing assistance for manuscript translation in English was provided by an independent medical writer, funded by SFRMS France.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.resmer.2024.101105.

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