



## SEPAR Guidelines

## Diagnosis and treatment of sleep apnea-hypopnea syndrome

### Diagnóstico y tratamiento del síndrome de apneas-hipopneas del sueño

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## Introduction

After the last recommendations of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) for the diagnosis and treatment of sleep apnea-hypopnea syndrome (SAHS) published in 1998 and the National Consensus Document on SAHS (in Spanish, DCNSAHS) by the Spanish Sleep Group (in Spanish, GES) in 2005, the intention of the current guidelines is to use the best evidence available to update the recommendations for the diagnosis and treatment of SAHS. SAHS is defined as an altered

apnea-hypopnea index (AHI > 5), accompanied by at least by snoring and/or witnessed apnea. The Grade system<sup>1</sup> has been followed (table 1) in order to establish recommendations (consistent or weak) depending on the quality of the evidence (high, moderate, low or very low) of the studies found in the literature.

The guidelines have been structured into 8 topics dealing with the definition, epidemiologic aspects, clinical aspects (including cardiovascular complications due to its special implication in making therapeutic decisions), diagnostic methods and treatment. In accordance with the evidence derived from recent, solid cohort studies demonstrating an increase in cardiovascular morbidity and mortality in SAHS patients, especially in those with AHI  $\geq$  30, these guidelines accept an AHI

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**Table 1**Classification of the recommendations and quality of evidence according to the Grade system<sup>1</sup>

Grade of recommendation	Quality of evidence	Implications
Consistent recommendation; <sup>a</sup> high quality of evidence	Well-done RCT, or exceptionally well done OS	Can be applied in most patients under most circumstances
Consistent recommendation; <sup>a</sup> moderate quality of evidence	RCT with limitations, or well done OS with important effects	Can be applied in most patients under most circumstances
Consistent recommendation; <sup>a</sup> low quality of evidence	Evidence for at least one important result of an OS, or RCT with important defects or very indirect evidence.	May change when evidence becomes available
Consistent recommendation; <sup>a</sup> very low quality of evidence	Evidence for at least one important result of non-systemic clinical observations or very indirect evidence	May change when greater evidence becomes available
Weak recommendation <sup>b</sup> ; high quality of evidence	Well-done RCT or exceptionally well-done OS	May differ depending on the circumstances or the patients
Weak recommendation <sup>b</sup> ; moderate quality of evidence	RCT with limitations, or well-done OS with important effects	Other alternatives may be better for some patients under certain circumstances
Weak recommendation <sup>c</sup> ; low quality of evidence	Evidence for at least one important result of OS, or RCT with important defects or indirect evidence	Other alternatives may be equally reasonable
Weak recommendation <sup>d</sup> ; very low quality of evidence	Evidence for at least one important result of OS, or RCT with important defects of indirect evidence	Other alternatives may be equally reasonable

OS: observational studies; RCT: randomized clinical trials.

<sup>a</sup>The benefits clearly outweigh the drawbacks, or vice-versa.<sup>b</sup>The benefits are in balance with the drawbacks.<sup>c</sup>Uncertainty in the estimation of the benefits or drawbacks; the benefits may be in balance with the drawbacks.<sup>d</sup>Major uncertainty in the estimation of the benefits or drawbacks; the benefits may or may not be in balance with the drawbacks.

≥ 30 as criteria for treatment, even in patients with few symptoms.

Obesity hypoventilation syndrome and Cheyne-Stokes respiration are sleep respiratory disorders that are frequently associated with SAHS, and are therefore reviewed in these guidelines. A chapter is dedicated to SAHS in children, whose diagnosis and prevalence are increasing, which will cause an increase in the activity of Sleep Units. Finally, we deal with the risk of accidents and the difficulty inherent in the concession and renovation of drivers' licenses in SAHS patients.

### Concept, Definitions, Severity, Pathogenesis and Epidemiology

The National Consensus Document on SAHS in 2005 defined SAHS as a combination of "symptoms including excessive

sleepiness and cognitive-behavioral, respiratory, cardiac, metabolic or inflammatory disorders secondary to repeated episodes of upper airway obstruction (UAO) during sleep<sup>2</sup> (consistent degree of recommendation, high quality of evidence). These episodes are measured with the apnea-hypopnea index (AHI) (table 2). An AHI > 5 associated with symptoms related with the disease and unexplained by other causes confirms the diagnosis<sup>2</sup> (consistent degree of recommendation, low quality of evidence). This definition is controversial. Considering an AHI > 5 as abnormal is arguable and it is probable that the threshold for abnormality differs, relating with sex and age (consistent recommendation, low quality of evidence). Moreover, the association of SAHS with excessive daytime sleepiness (EDS) was established arbitrarily.

EDS is an easily-measured symptom that is quite prevalent among the general population,<sup>3,4</sup> therefore AHI > 5 and EDS are,

**Table 2**

Accepted definitions for the main respiratory events, recommended by the National Consensus Document on sleep apnea-hypopnea syndrome

Obstructive apnea	Absence or reduction > 90% of the respiratory signal (thermistors, nasal cannula or pneumotachography) for > 10 seconds in presence of respiratory effort detected by thoracoabdominal movement
Central apnea	Absence or reduction > 90% of the respiratory signal (thermistors, nasal cannula or pneumotachography) for > 10 seconds in absence of respiratory effort detected by thoracoabdominal movement
Mixed apnea	A respiratory event that usually begins with a central component and ends with an obstructive component
Hypopnea <sup>a</sup>	A discernible reduction (> 30% and < 90%) in the width of the respiratory signal of > 10 seconds or an evident reduction in the thoracoabdominal result accompanied by desaturation (≥ 3%) and/or micro-arousal on EEG
Respiratory effort-related arousals (RERA)	Period > 10 seconds of progressive increase in respiratory effort (ideally detected by a progressive increase in esophageal pressure that ends with a micro-arousal (no evident reduction in flow – hypopnea criterion-). It can also be detected by short periods of flow limitation – flattening of the signal from the nasal catheter or reduction in the thoracoabdominal sum accompanied by micro-arousal)
Apnea-hypopnea index (AHI) <sup>b</sup> Respiratory disturbance (RDI) <sup>b</sup>	Sum of the number of apneas and hypopnea (the most frequently used parameter to evaluate the severity of sleep respiratory disorders. It is the number of apneas + hypopneas + RERA per hour of sleep (or per hour of tracing if respiratory polygraph is used). RDI is <i>Respiratory Disturbance Index</i> , as found in the literature
Definition of SAHS: SAHS = 1 + (A or B)	1. RDI > 5 associated with one of the following symptoms A. Excessive daytime sleepiness (ESD) unexplained by other causes B. Two or more of the following B1. Repeated asphyxia during sleep B2. Recurring arousals during sleep B3. Perception of sleep as non-restful B4. Tiredness and/or fatigue during the day B5. Difficulties for concentrating

Modified reproduction, with the permission of the Spanish Sleep Group (GES).<sup>1</sup> Definition of SAHS according to the American Academy of Sleep Medicine.<sup>2</sup><sup>a</sup>There is no well-contrasted definition of hypopnea, and there is no universal consensus for its definition; <sup>b</sup>from a practical point of view, AHI and RDI can be considered superimposable terms. In other words, RERA are included with hypopnea.

due to their high prevalence, concurring elements that are not necessarily associated. In addition the majority of the studies do not find an association between AHI and EDS,<sup>3</sup> suggesting that SAHS has a pluri-phenotypic expression in subjects responding to the classic definition (high AHI and EDS), with or without secondary complications, while in others there may be complications without symptoms or instead, exclusively high AHI (consistent degree of recommendation, low quality of evidence). Therefore, taking into account all the available data, the presence of AHI > 15 is associated with an increase in cardiovascular risk, with or without associated symptoms, and this risk is much greater in patients with AHI > 30. These data strongly suggest that the definition of SAHS should be based, first and foremost, on the observance of an abnormal AHI and it is so recognized in the recent recommendations of the *American Academy of Sleep Medicine*.<sup>5</sup>

### Physiopathology

The physiopathological mechanisms of SAHS are not thoroughly understood, and a multifactorial origin is suggested, where anatomical and functional factors interact (consistent degree of recommendation, moderate quality of evidence). The collapse of the UA would result as a consequence of an imbalance between those forces that tend to close it and those that maintain it open. It is accepted that there are factors that tend to close the lumen of the UA secondary to a deficiency in its reflexes, either in the respiratory centers or in the musculature itself of the UA, causing the different respiratory events and secondary biological and physiopathological disorders, and a genetic and environmental basis for these has been suggested (consistent recommendation, low quality of evidence).

### Epidemiology

SAHS is a very prevalent disease in the general population that may cause deterioration in quality of life, arterial hypertension, traffic accidents and cardiovascular and cerebrovascular diseases, and is related with excess mortality.<sup>1,2,6-9</sup> (consistent recommendation, high quality of evidence). Furthermore, it has been demonstrated that undiagnosed patients double the expenditure of health care resources compared with diagnosed and treated patients.<sup>10,11</sup> For these reasons, SAHS is considered a first-rate public health problem. In Spain, between 3 and 6% of the population suffers from symptomatic SAHS and between 24 and 26% AHI > 54.

As for risk factors, age, masculine sex and body mass index are the most important. The prevalence of SAHS increases with age, tripling in senior patients when compared with middle-aged subjects. Likewise, the male/female ratio of middle-aged patients is 2-3/1, tending to become more equal after menopause. Other variables that influence the appearance of SAHS or its severity are alcohol, tobacco, sedatives, hypnotics and barbiturates, and the supine decubitus position. Other important factors are related to genetics, family and ethnic group (consistent recommendation, high quality of evidence). Regarding the severity classification, this is established as: mild (AHI: 5-14.9); moderate (AHI: 15-29.9); severe (AHI > 30)<sup>12</sup> (consistent recommendation, low-moderate quality of evidence).

It is expected that the development of personalized medicine will allow us to identify what genetic factors condition the appearance of SAHS, as well as for whom high AHI is a specific health risk that we can quantify and differentiate from those

**Table 3**  
Most frequent symptoms and signs of SAHS

Symptoms and frequent signs	Anamnesis and basic physical examination
Thunderous snoring	History of interest (especially cardiopulmonary)
Witnessed apnea	Symptoms related to SAHS (Epworth scale)
Excessive daytime sleepiness	Sleep habits (Schedule, naps, sleep hygiene)
Non-restful sleep	Anthropometric variables (BMI, neck and waist perimeter)
Wide, short neck	Hyoid-to-mandible distance (short neck)
Obesity	Routine ORL examination
Episodes of nocturnal asphyxia	Nasal obstruction
Frequent arousals	Hypertrophy of tonsils or uvula
Nocturia	Long soft palate
Morning headache	Mallampati degrees
Arterial hypertension	Examination of the maxilla and mandible (retro-micrognathia)
	Bite quality
	Cardiopulmonary auscultation
	Blood pressure

BMI: body mass index; ORL: otorhinolaryngological.

others that, due to genetic characteristics, are more protected against the consequences of SAHS. This will allow us to design interventions that will influence prevention and treatment. Currently, we are still guided by the epidemiological risk, which indicates that high AHI implies potential damage to patient health.

### SAHS Clinical Symptoms and Physical Examination

The symptoms related with SAHS appear to be a consequence of two fundamental physiopathological facts: on one hand, intermittent apnea, hypopnea and hypoxia, and on the other unstructured sleep.<sup>2</sup> The most frequent symptoms and signs, be they diurnal or nocturnal, are shown in table 3. No clinical parameter, either isolated or in combination with others, has demonstrated enough value to diagnose SAHS, as they may also frequently appear in healthy individuals or be absent in SAHS patients (consistent recommendation, high quality of evidence). Exhaustive clinical evaluation and physical exploration are necessary as they allow us to classify the patients with high, medium or low pretest clinical probability (fig. 3: diagnostic methods), which is essential for later evaluating the diagnostic method to use, (consistent recommendation, low quality of evidence). The main clinical triad for SAHS is made up of 3 symptoms:<sup>13</sup>

- *Chronic snoring*: this is the symptom with greatest sensitivity (its absence makes the diagnosis of SAHS improbable). However, the majority of snorers do not have SAHS (40% of men and 20% of women snore in the general population). Therefore, the presence of chronic snoring as the only symptom is not enough to carry out a sleep test with the intention of diagnosing SAHS.
- *Witnessed apneas*: this is the symptom with greatest specificity, which increases if the apneas are observed repeatedly over the course of the same night and if they are prolonged.
- *Excessive daytime sleepiness or tendency to fall asleep involuntarily in inappropriate situations*: not very specific or sensitive symptom, but the most important as it marks the clinical intensity of SAHS. Its presence, unexplained by evident circumstances, is sufficient even in the absence of other symptoms or signs to carry out a sleep study for diagnosis. It is important to rule out other causes of hypersomnia (table 4).

**Table 4**  
Differential diagnosis of hypersomnia

Behavior disorders	Poor sleep hygiene, (insufficient sleep, interrupted sleep timetable, etc.)
Psychiatric diseases	Mood disorders, psychosis, etc.
Environmental factors	Environmental sleep disorder, toxins, etc.
Drug addictions	Alcoholism, hypnotic drugs, stimulants, etc.
Sleep respiratory alterations	SAHS, apnea central, central alveolar hypoventilation, sleep-related neurogenic tachypnea, etc.
Abnormal movements	Periodic leg movements, etc.
Wakefulness-sleep alterations	"Big sleepy-head", jet lag, night jobs, phase delay syndrome, advanced phase syndrome, non-circadian schedules, irregular wakefulness-sleep pattern, etc.
Other CNS alterations	Narcolepsy, idiopathic hypersomnia, recurring hypersomnia, sub-wakefulness syndrome, fragmentary myoclonus, parkinsonisms, dementia, sleeping disease, etc.
Other causes	Menstruation, pregnancy, etc.

Measuring hypersomnia can be done by means of subjective or objective methods. Among the subjective methods, the most widely used is the Epworth questionnaire.<sup>14</sup> The presence of a score equal to or more than 12 points (out of 24 points) indicates pathological hypersomnia. Even though there are cultural, age and sex variations and there is limited correlation with the objective measurements, it is useful especially in the follow-up of patients with repeated measurements. Due to its simplicity, the classification in degrees of hypersomnia can also be used (mild, moderate or severe). Objective methods include the multiple sleep latency test (MSLT), maintenance of wakefulness test (MWT), the Osler test and the motor skills wakefulness test.

Table 3 includes the most frequent signs and symptoms related with SAHS, as well as the basic exploration and anamnesis necessary. Other frequent symptoms and signs that do not appear in the table (occasionally related to patient age and sex) are: diaphoresis, nightmares, restless sleep, insomnia, gastroesophageal reflux, enuresis, decreased libido, personality changes, loss of memory, difficulty in maintaining concentration, affected work/study performance, apathy, irritability, morning nausea, symptoms of depression, chronic tiredness, abnormal movements, frequent falls, cardiovascular events, polyglobulia and epileptic crises.

The SAHS guidelines recommend ordering a metabolic analysis profile including hemogram, basic biochemistry and lipid profile for all patients. Chest radiography, electrocardiogram, thyroid hormone levels and forced spirometry should only be ordered in cases with suspicion of concomitant disease.

#### SAHS in Seniors

The number of respiratory sleep disorders undergoes a linear increase with age, either due to aging itself (increased collapsibility of the airway) or due a true pathological situation (SAHS).<sup>15</sup> The cut-point at which AHI should be considered pathological is currently undetermined. This is a problem with special epidemiological importance given the growing longevity of the population. SAHS symptoms occasionally differ from the usual symptoms as the impact of SAHS in seniors can be more centered in the neurocognitive sphere.<sup>16</sup> The Epworth questionnaire results must be evaluated carefully as this test has not been validated in seniors. Moreover, there are no studies

**Table 5**  
Patients with high risk for SAHS in whom related symptoms should be evaluated

Obesity (BMI > 35)
Cardiac insufficiency
Atrial fibrillation
Refractory hypertension
Type 2 diabetes mellitus
Nocturnal arrhythmias
Cerebrovascular accidents
Pulmonary hypertension
Individual with high risk for accidents
Pre-operative bariatric surgery
Chronic respiratory diseases with greater gasometric deterioration than expected

with sufficient levels of evidence analyzing the effect of CPAP treatment or other treatments in older patients.<sup>17</sup> The current recommendation is that, in the diagnosis and treatment of SAHS in seniors, age is not itself (except in extreme situations) an obstacle (consistent recommendation, low quality of evidence). A trial with CPAP for some months with later evaluation of the clinical response can be a good alternative in case of doubt. It is unknown whether there is an age after which CPAP could be withdrawn, thus at this time it is not recommended.

#### SAHS in Women

In the general population, the prevalence of SAHS in women is less than in men, but there is a greater percentage of cases gone undiagnosed. In post-menopausal women, the prevalence increases and reaches the same prevalence as in men. There is little scientific evidence related to SAHS in women. The clinical presentation can vary compared to the typical symptoms in men, especially in a higher frequency of symptoms of depression, anxiety, general fatigue, lack of energy and headache. It is important to keep these clinical variations in mind when deciding the pretest clinical probability of the patient and the diagnostic method to use.<sup>18</sup> The impact of SAHS in women could also be different than in men, especially in pre-menopause, modulated by the hormonal state. However, it is currently recommended that diagnosis and treatment of SAHS should not vary from those used in men (consistent recommendation, low quality of evidence).

Table 5 shows a list of diseases or risk situations that can be associated with SAHS and in which anamnesis of symptoms compatible with SAHS should be done.

#### Cardiovascular Consequences; Morbidity and Mortality; Surgical Risk

SAHS is associated with varying degrees of hypoxemia, hypercapnia, reduction in intrathoracic pressure and cortical and sympathetic activation. These events induce intermediate mechanisms that potentially favor the development of cardiovascular and metabolic disease and premature death (fig. 1). This chapter summarizes the evidence available on the cardiovascular consequences (intermediate disease mechanisms) and the associated cardiovascular morbidity and mortality.

#### Cardiovascular Consequences of SAHS

During apnea, the hypoxemia-hypercapnia stimulates chemoreceptors and the lack of breathing blocks the sympathetic inhibition afferent from the thorax. Both mechanisms increase

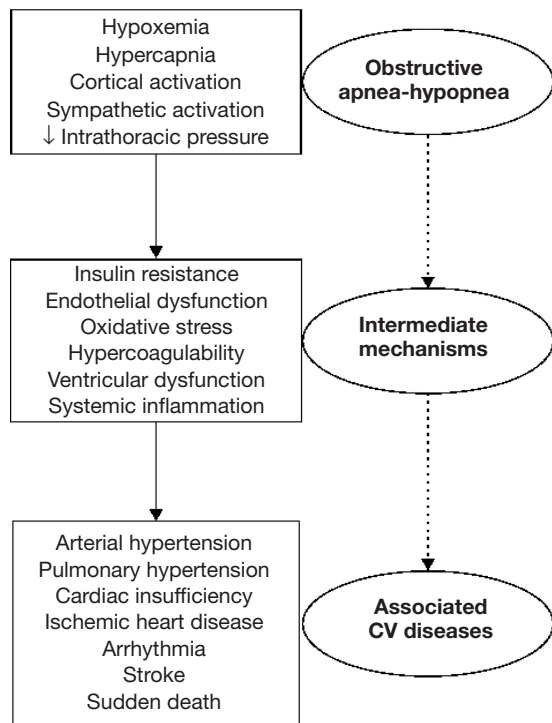


Figure 1. Physiopathogenic mechanisms of the cardiovascular consequences of SAHS.

the sympathetic outflow that at the same time is responsible for generalized vasoconstriction, increase in arterial pressure and increase in the myocardial consumption of O<sub>2</sub> (high quality of evidence).<sup>19</sup> The obstruction of the pharynx induces inefficient inspiratory effort. This then generates very negative intrathoracic pressures that increase the transmural pressure of the left ventricle and the venous return to the right heart. Then the interventricular wall is displaced towards the left, increasing the preload of the right ventricle and the postload of both ventricles. The final consequence is the reduction in systolic volume and the absence of diastolic relaxation. Treatment with CPAP in patients with SAHS and cardiac insufficiency reverts these phenomena (consistent recommendation, moderate quality of evidence).<sup>20</sup>

The repetitive episodes of deoxygenation and reoxygenation induce the excessive production of oxygen free radicals, proinflammatory cytokines, circulating inflammatory cells, C-reactive protein and endothelial adhesion molecules. These changes promote generalized endothelial lesions and favor the development of atherosclerosis (high quality of evidence).<sup>21</sup>

Regardless of body mass index (BMI), SAHS patients show high resistance to circulating insulin and greater risk for developing type 2 diabetes (high quality of evidence). However, the results of a randomized study did not demonstrate that CPAP significantly improved the control over glycemia or resistance to insulin in males with type 2 diabetes and SAHS.<sup>22</sup>

#### Cardiovascular Morbidity

– **Hypertension.** 50% of SAHS patients have hypertension and 80% of patients with resistant hypertension have SAHS. There is a direct relationship between the severity of SAHS and the probability of hypertension, and SAHS is a causal factor for AH. In randomized studies controlled with placebo, CPAP significantly reduces AH mainly in patients with severe SAHS

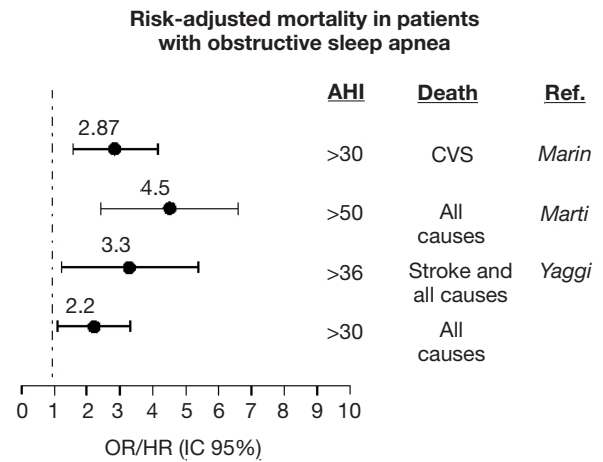


Figure 2. Risk of mortality.

who have hypertension and with good CPAP compliance (consistent recommendation, moderate quality of evidence).<sup>23</sup>

- **Cardiac insufficiency.** The prevalence of cardiac insufficiency (CI) in SAHS patients is higher than 10%. The studies available indicate a significant improvement in the LV ejection fraction, reduction in the number of hospitalizations and increased survival in patients with CI-SAHS that tolerate and use CPAP (consistent recommendation, moderate quality of evidence).<sup>20</sup>
- **Arrhythmia.** The prevalence of all types of arrhythmias, especially atrial fibrillation (AF) is increasing in patients with SAHS. CPAP treatment in patients with SAHS and AF reverted by cardioversion is followed by a reduction in the probability of AF recurrence (consistent recommendation, moderate quality of evidence).<sup>24</sup>
- **Ischemic heart disease.** Population studies with a clinical base have demonstrated an independent association between the degree of SAHS and the probability of CI. This excess risk compared with the healthy population occurs above all in people under the age of 50 and is independent of BMI (moderate quality of evidence).<sup>25</sup>
- **Stroke.** Epidemiological studies indicate that the probability of stroke in patients with SAHS is from 1.6 to 4.3 times greater than subjects without SAHS (moderate quality of evidence).<sup>26</sup>

#### Cardiovascular Mortality

No causal relationship has been demonstrated between SAHS and cardiovascular mortality. Cross-sectional prospective population studies show an association between SAHS and an excess of cardiovascular mortality. Numerous cohort studies, both population and clinical, over a period of 10 years confirm this association, especially for patients with severe SAHS (ex. AHI > 30) and in the middle decades of life (ex. 30-60 years). This excess in mortality has been especially related with death by ictus or myocardial infarction (fig. 2) (consistent recommendation, moderate quality of evidence).<sup>9,27,28</sup> In cohort studies, treatment with CPAP reduces this excess of cardiovascular mortality in patients with severe SAHS and good compliance (consistent recommendation, moderate quality of evidence).<sup>9,27-29</sup>

#### Surgical Risk

SAHS patients who need to undergo surgery with general anesthesia present greater risk of perioperative complications,

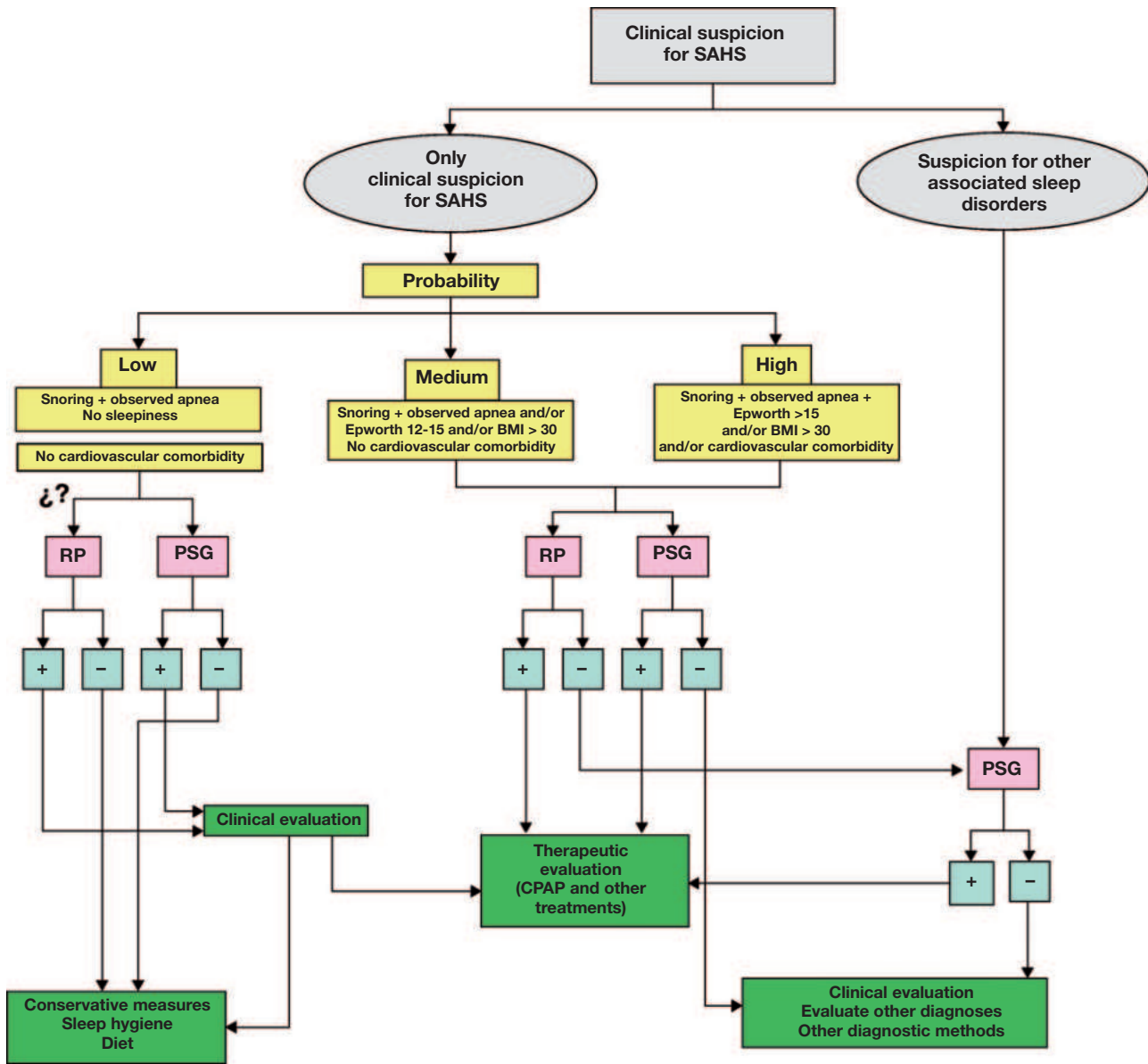


Figure 3. Flowchart of steps for SAHS suspicion. PSG: conventional polysomnography; RP: respiratory polygraphy (either at home or in the hospital).

especially due to the effects of the anesthesia on ventilatory control and on the muscle tone of the upper airway. The application of nasal CPAP after extubation and the placement of the patient in semi-sitting position are general post-operative recommendations (consistent recommendation, low quality of evidence).

**Diagnostic Methods; Indications**

Conventional polysomnography (PSG) observed by a technician in the sleep laboratory is the reference method for the diagnosis of patients with suspicion for SAHS and other non-respiratory sleep disorders (consistent recommendation, high quality of evidence).<sup>2,30</sup> This consists of continuous tracings from electroencephalogram, electrooculogram and mentonian electromyogram (in order to quantify the sleep phases and micro-awakenings), as well as other variables to quantify respiratory disorders and their repercussions (pulse-oximetry,

oronasal airflow using nasal cannula and thermistor, snoring, thoracoabdominal movements and electrocardiogram). PSG should be done either at night or during the subject's usual sleep schedule, with a register of no less than 6.5 hours, including at least 3 hours of sleep. PSG is a relatively expensive, laborious and technically complex technique that is not available at all centers, and due to the large demand of examinations it cannot be used in all patients.

In order to deal with these difficulties, portable equipment has been developed to register only the respiratory variables, therefore this technique is called respiratory polygraphy (RP). The American Academy of Sleep Medicine (AASM) has classified sleep studies into 4 types.<sup>31</sup> Type 1 is conventional PSG overseen by a technician in a sleep laboratory (with a minimum of 7 channels); type 2 is PSG done with portable equipment and no technician present; type 3 is so-called RP, where breathing, thoracoabdominal effort and pulse-oximetry are recorded (with a total of 4-7 channels); and type 4 are super-

simplified studies with a 1-2 channel apparatus (oximetry and/or breathing).

Despite the large number of studies confirming the utility of RP (for hospital as well as home use),<sup>32</sup> in the last two years two important documents have been published in the United States, where, after an exhaustive review of the literature, the use of home RP has finally been approved. The first, published by the AASM,<sup>33</sup> concludes that the unobserved registers with type-3 monitors (RP) can be used as an alternative to PSG in patients with a moderate or high probability of SAHS. In the second, an official document by Medicare,<sup>34</sup> type-2, -3 or -4 monitors (with at least 3 channels) are accepted as diagnostic methods in order to prescribe CPAP.

Therefore, we consider PR (at the hospital as well as at home) to be an acceptable method in order to confirm diagnosis in patients with moderate or high clinical suspicion for SAHS (consistent recommendation, moderate quality of evidence). The use of RP for those cases with low probability of SAHS is not validated, although it does form part of standard clinical practice. RP reduces health-care costs and waiting times, and makes the diagnosis of SAHS accessible to centers that do not have conventional PSG available (basic Sleep Units according to SEPAR accreditation).<sup>35</sup> The disadvantages of RP: it does not evaluate the quality of sleep, respiratory disorders are underestimated (expressed per hour of tracing instead of hours of sleep), and other non-respiratory sleep disorders cannot be evaluated. Home RP has the advantage that the patient sleeps in his/her own bed, thus the sleep pattern is more representative of everyday sleep.

Regarding the super-simplified systems (type 4 monitors), there are no validation studies recommending their use (weak recommendation, low quality of evidence). Nocturnal oximetry can demonstrate the presence of apnea or hypopnea, but it does not distinguish among the central obstructive disorders nor does it detect events without desaturation, and therefore its use as a diagnostic method is not recommended. Recent studies on monochannel systems with flow<sup>36,37</sup> or bichannel systems with flow and saturation<sup>38</sup> suggest that they could play a role in the diagnosis of SAHS.

Current digital equipment can automatically analyze signals, but the tracings should be reviewed and/or analyzed manually by specialists with expertise in respiratory sleep disorders and PSG (consistent recommendation, high quality of evidence), as automatic analysis is not reliable.

Before the diagnostic tests, a complete clinical evaluation of the patient should be carried out (especially in sleep disorders) by a specialist with experience in these disorders in order to decide what type of study would be the most adequate. If there is clinical suspicion of SAHS and the RP is negative or technically deficient, PSG should be done. Health-care centers that only have RP available should work together in coordination with reference units that have PSG (Multidisciplinary Units or Respiratory Units, according to SEPAR accreditation)<sup>35</sup> so that these better-equipped units can help them resolve cases in which RP is not enough. Figure 3 summarizes the diagnostic strategy recommended in cases suspected of SAHS.

If there is suspicion for other associated sleep disorders, PSG should be performed. If there is only suspicion of SAHS, RP can be done as well as PSG. If the RP is negative and the clinical probability for SAHS is moderate or high, PSG should be carried out. The use of RP to rule out SAHS in cases with low probability, although part of standard clinical practice, has not been validated and therefore its usage is questionable.

## Central Apnea, Cheyne-Stokes Breathing, Overlap Syndrome, Hypoventilation-Obesity Syndrome

### Central Apnea

Central apnea (CA) and central hypopnea are caused by either the absence of or diminished inspiratory effort and are usually triggered when PaCO<sub>2</sub> drops below the apneic threshold. In order to correctly evaluate hypopnea, esophageal pressure measurements are necessary. SAHS is considered central if  $\geq 50\%$  of events are central and are accompanied by symptoms. Idiopathic CA occurs in  $< 5\%$  of SAHS patients, but those secondary to cardiac insufficiency represent 40-80%. CA can have presentation with diurnal hypercapnia (alteration in ventilatory or respiratory muscle control) or with normocapnia (transitory instability of ventilatory control).<sup>39</sup>

The increase in mortality derived from CA in cardiac insufficiency is controversial (weak recommendation, moderate quality of evidence). Diagnosis is recommended by means of PSG. There is not enough evidence to recommend a specific treatment. The first step is to optimize the treatment of the underlying disease and, if CA persists, try CPAP (CA without hypercapnia) (weak recommendation, moderate quality of evidence). CPAP improves left ventricular ejection fraction and AHI, without improving survival, and the efficacy of CPAP should be confirmed (residual AHI  $< 15$ ) or if not it should be suspended.<sup>40</sup> Clinical assays with adaptive servoventilation (ASV) demonstrate better tolerance and greater reduction in CA (weak recommendation, moderate quality of evidence). In CA with hypercapnia, non-invasive ventilation (NIV) can be used (weak recommendation, low quality of evidence).

There is a type of CA observed in CPAP (sleep apnea complex, or "CompSAS"), that is produced either by the disappearance of the obstructive events that hid it or due to the hypocapnic effect of CPAP (apneic threshold). Its presence could result in the persistence of symptoms (weak recommendation, low quality of evidence) and disappear with maintained CPAP or ASV treatment<sup>41</sup> (weak recommendation, moderate quality of evidence).

### Cheyne-Stokes Breathing

This involves CA or hypopnea with periodic oscillations in ventilation, frequently associated with cardiac insufficiency (also with ictus and sedation). Ventilation rises and falls progressively to the point of CA or hypopnea, a cycle which reinitiates every 60-90 seconds, causing intermittent hypoxia. This worsens the prognosis of the cardiac insufficiency and increases mortality<sup>42</sup> (consistent recommendation, moderate quality of evidence). Treatment consists of optimizing the treatment of the underlying disease and trying out CPAP, although the effects on survival have not been demonstrated<sup>40,42</sup> (weak recommendation, moderate quality of evidence). ASV seems to show an improvement in somnolence and neurohormonal activation (weak recommendation, moderate quality of evidence).

### Overlap Syndrome

This is the concurrence of SAHS and COPD. The prevalence of SAHS in COPD patients is no greater than in the general population.<sup>43</sup> Clinically, the patients present more sleepiness and nighttime desaturation, more risk of right cardiac insufficiency, hypercapnic respiratory insufficiency and pulmonary

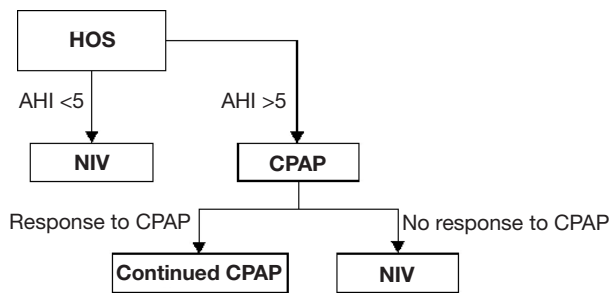


Figure 4. Choice of treatment.

hypertension. These consequences can contribute to a greater risk of mortality<sup>44</sup> (weak recommendation, low quality of evidence). The diagnostic method recommended is PSG. The treatment consists of oxygen therapy if the criteria for this therapy are met (consistent recommendation, high quality of evidence), and trying CPAP to eliminate obstructive events and nocturnal desaturation, which can lead to an improvement in the survival of more severe hypoxemic COPD and SAHS patients<sup>45</sup> (weak recommendation, low quality of evidence). In patients with hypercapnia, NIV can be necessary (weak recommendation, low quality of evidence). No greater survival has been demonstrated with exclusively nocturnal oxygen therapy for treating persistent nocturnal desaturation<sup>46</sup> (consistent recommendation, high quality of evidence).

#### Hypoventilation-Obesity Syndrome (HOS)

HOS is the concurrence of diurnal hypoventilation ( $\text{PaCO}_2 > 45$  mmHg) and obesity ( $\text{BMI} > 30$ ) when other causes of hypercapnia can be excluded. Close to 90% of these patients suffer from sleep apnea. The prevalence of HOS is unknown, although it may affect a minority of the obese population. The prevalence of HOS in subjects with suspected SAHS varies between different studies (from 10 to 30%).

Weight loss is the ideal treatment. A return to normal weight reverts respiratory insufficiency, pulmonary hypertension and sleep alterations (consistent recommendation, low quality of evidence), but it is difficult to achieve. Bariatric surgery is an alternative for a minority of patients, given its high morbidity and mortality (weak recommendation, low quality of evidence). NIV produces improvements in symptoms, gasometry and sleep alterations and a decrease in days of hospitalization<sup>47</sup> (consistent recommendation, moderate quality of evidence). There are no controlled assays that have studied mortality.

CPAP corrects apneic events, but daytime  $\text{PaCO}_2$  does not normalize in all cases. Apnea time could be a marker for CPAP efficacy.<sup>48</sup> CPAP and NIV have similar short-term effects in patients selected by a favorable response to a night of CPAP treatment<sup>49</sup> (consistent recommendation, moderate quality of evidence). There are no similar studies in unselected patients or on whether these treatments are more effective than weight loss. Until more evidence is available, we can follow the following flowchart in figure 4.

Patients with HOS and pathological AHI would be initially treated with CPAP. If nocturnal or diurnal hypoventilation exists (non-responsive), NIV would be the best treatment option. In the case of an initial improvement with CPAP (responsive), the patients would continue with the same treatment. Patients with HOS without pathological AHI would be directly treated with NIV.

Table 6

Etiological/coadjuvant factors of sleep apnea-hypopnea syndrome, modifiable with treatment

Poor sleep hygiene (irregular and insufficient)
Obesity
Sleep position
Intake of sedatives or alcohol and tobacco habit
Nasal blockage (due to rhinitis, fundamentally)
Anatomical factors such as adenoid and/or tonsillar hypertrophy, bone malformations or deformities (basically mandibular), anatomical nasal obstruction
Metabolic diseases that can be associated with SAHS, such as hypothyroidism or acromegaly

#### SAHS Treatment and Follow-up: Criteria and Therapeutic Options

The objectives of the treatment are, on one hand, to gain control over the symptoms (fundamentally sleepiness) and on the other to minimize the cardiovascular risk and risk of accidents. With regards to which treatment to recommend, and based on the fact that nasal CPAP is the first-choice treatment in most cases (consistent recommendation, high quality of evidence), the presence of modifiable concomitant etiological factors should also be taken into account (table 6) and the pertinent treatment should be ordered, either alone or in conjunction with nasal CPAP. Patients diagnosed with SAHS, regardless of the treatment recommended, require medical follow-up.<sup>2,5</sup>

We will consider the following therapeutic options:

##### 1. Sleep hygiene measures (consistent recommendation, moderate quality of evidence)

Proper sleep hygiene is important as the most frequent cause of excessive daytime sleepiness is poor sleeping habits, specifically either insufficient or irregular sleep. We will also consider: alcohol and tobacco abstinence, avoidance of benzodiazepines (if sleep inducers are necessary, non-benzodiazepine hypnotics should be used) and sleeping in decubitus supine (apply physical impediment on the back if necessary). Raising the head 30° can also be useful.

##### 2. Diet (consistent recommendation, moderate quality of evidence)

Weight loss in obese patients can be curative. A weight reduction of 10% can reduce AHI and improve symptoms. We should recommend diet and change of lifestyle to patients with  $\text{BMI} > 25$ . In patients with morbid obesity ( $\text{BMI} > 40$ ), bariatric surgery can be evaluated in an adequate context.

##### 3. Other conservative treatments (consistent recommendation, low quality of evidence)

a) *Pharmacological treatment of nasal obstruction*: nasal congestion can be factor that worsens SAHS. Its treatment with nasal corticosteroids can improve SAHS and, especially, tolerance of nasal CPAP. b) *Quality of evidence*: a reduction in AHI has been observed after substitutive treatment. c) *Quality of evidence*: not recommendable if there is no respiratory insufficiency associated with SAHS or for other cardiac or respiratory motives which persist after 3 months of nasal CPAP treatment. d) *Quality of evidence*: currently without indication. Protriptyline and medroxyprogesterone are in disuse, and selective serotonin reuptake inhibitors are still in research phase. e) *Quality of evidence*: there is no evidence of clear improvement. f) *Quality of evidence*: it is questioned whether the treatment can improve SAHS.



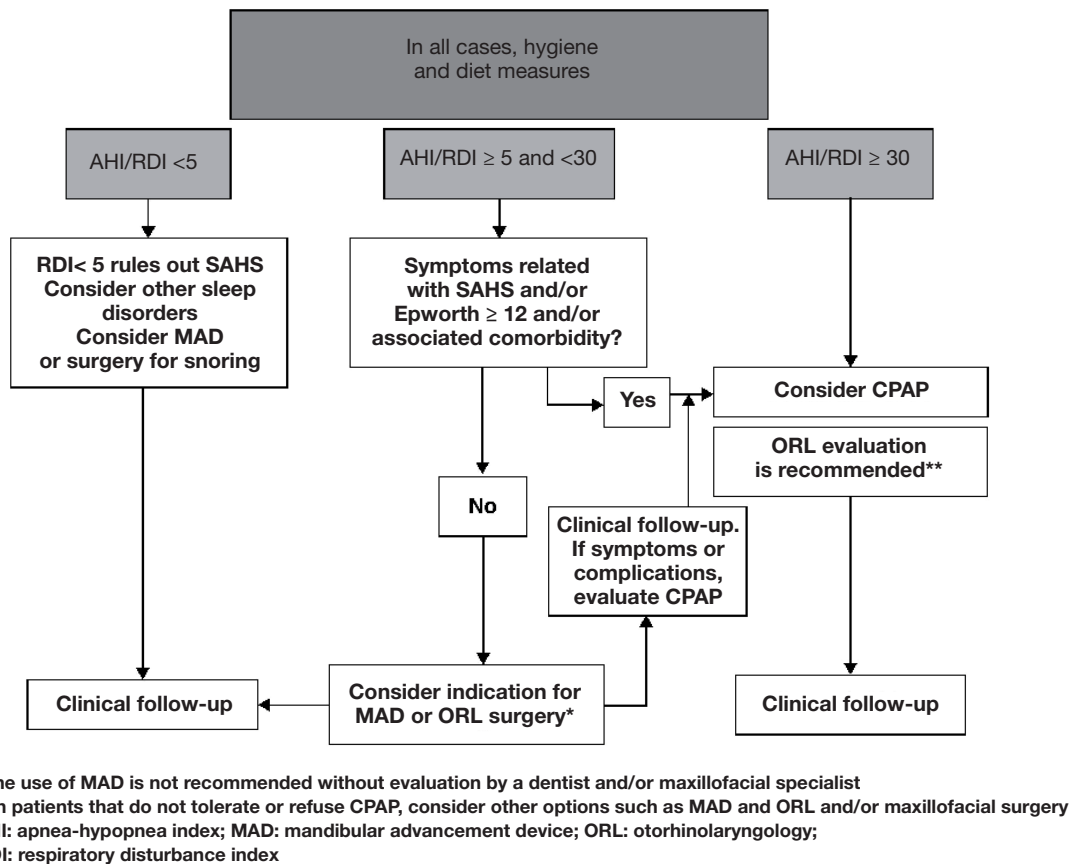


Figure 5. Treatment guidelines: algorithm. Adapted from the DCNSAHS, GES.<sup>2</sup>

#### 4. Treatment with nasal CPAP

##### 4.1. Effects

Nasal CPAP is more effective than placebo for improving sleepiness and quality of life in patients with SAHS. It corrects obstructive phenomena, snoring, desaturations and arousals secondary to respiratory events, sleep architecture, attention capacity (among other cognitive variables), reduces risk for traffic accidents and normalizes blood pressure readings in a percentage of hypertensive patients. Bi-pressure systems do not demonstrate clear advantages.<sup>50</sup>

##### 4.2. Indications

The indications for treatment with nasal CPAP are reflected in the DCNSAHS algorithm (fig. 5).<sup>2</sup> Patients with  $AHI \geq 5$  and symptoms (excessive somnolence) are susceptible to nasal CPAP treatment. If they are asymptomatic, with or without cardiovascular disorder, treatment should be considered with an  $AHI \geq 30$ , especially in patients under the age of 70<sup>51</sup> (consistent recommendation, high quality of evidence).

##### 4.3. Adjustment of optimal pressure

It is essential for the patient to be given adequate information and preparation. Different techniques can be used for the adjustment. Complete PSG best assures the correction of all the pathological phenomena (respiratory and neurological). Other options are half-night PSG for patients with  $AHI > 20$ , the empirical adjustment made by means of mathematical formula, that can be used provisionally until titration,<sup>52</sup> and a validated self-CPAP system with visual analysis<sup>52</sup> (consistent recommendation, moderate quality of evidence).

##### 4.4. Side effects

These usually appear in the first week and are minor and transitory. The most common are nasal congestion, skin irritation, pharyngeal dryness and cold (improved with the introduction of a humidifier-heater), noise, conjunctivitis, epistaxis, insomnia and aerophagia.

The only absolute contraindication is fistula of cerebrospinal liquid and should be used with precaution in all those situations that can worsen with the administration of positive pressure.

##### 4.5. Follow-up

As nasal CPAP is not a curative treatment, it should be used continuously. The minimal compliance associated with a clear improvement in symptoms is 3.5 h/night. Therefore, in all patients with a compliance of less than 3 h/night, the possible causes and the improvement in symptoms should be investigated. In these cases, the decision to withdraw the treatment due to poor compliance should be individualized. Follow-up consultations are recommended at one month, every 3 months during the first year, after 6 months in the second year, and then yearly or whenever the patient requires a consultation (consistent recommendation, low quality of evidence). In the event of significant weight loss or weight gain (10%) or reappearance of symptoms related with SAHS a new CPAP titration study is indicated.

#### 5. Mandibular advancement devices (MAD)<sup>53</sup>

These are effective in the treatment of snoring, mild and moderate SAHS with low BMI and unimportant desaturations

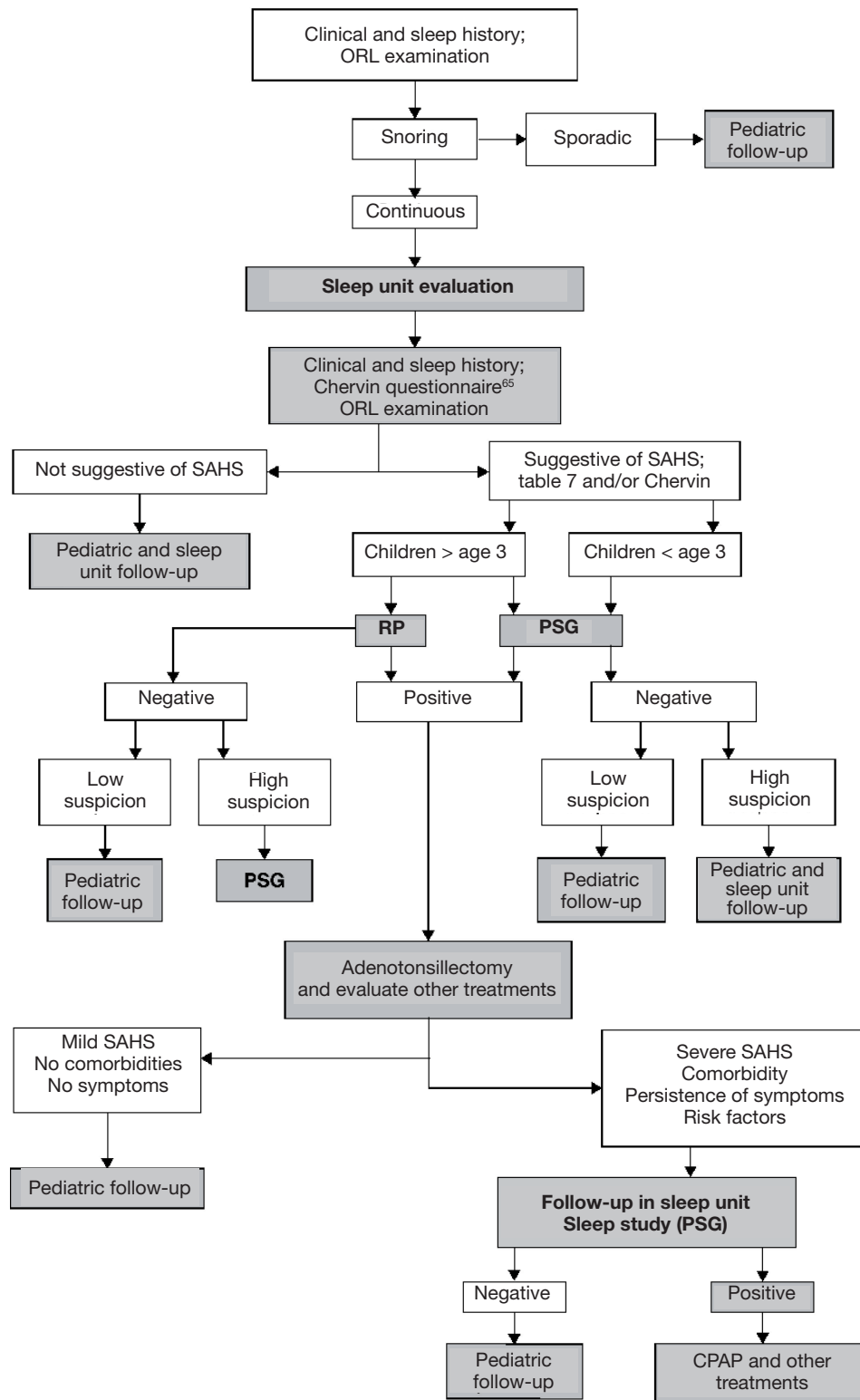


Figure 6. Decision flowchart in childhood SAHS.

(consistent recommendation, moderate quality of evidence). They can also be useful in patients with increased upper airway resistance syndrome and as a second choice in patients that do not tolerate nasal CPAP who are not candidates for surgery or have high surgical risk. There are devices with set advancement and those with regulatable advancement. Certain cephalometric characteristics improve the performance

of the MAD. Progressive regulation is recommended, along with polysomnographic control of its effects.

## 6. Surgical treatment<sup>54</sup>

### 6.1. Nasal surgery

This does not resolve SAHS independently. It should be considered especially in those cases of intolerance to nasal CPAP due to obstruction.

**Table 7**

Symptoms and signs suggestive of SAHS in children

Nighttime	Daytime
Continuous snoring (not only in exacerbation)	Normal
Observed respiratory pauses	Daytime oral breathing, nasal voice, adenoid facies
Noisy breathing	Tonsillar hypertrophy
Oral breathing	Facial dysmorphism (retrognathia, micrognathia, macroglosia, midfacial hypoplasia)
Increased respiratory effort (supra-sternal and intercostal retraction)	Difficulty to wake up, tiredness upon getting up, morning headaches, daytime sleepiness
Nocturnal sweating	Alterations in behavior (hyperactivity, aggressiveness, irritability, low school performance level)
Abnormal sleep posture (hyper-extension of the neck)	Delayed growth and low height/weight development
Restless nocturnal sleep	Obesity
Cyanosis	Strong second heart sound
Nocturnal enuresis	Systemic arterial hypertension
	Presence of metabolic syndrome

### 6.2. Oropharyngeal surgery

This can be carried out by means of conventional surgery, laser or radiofrequency techniques, depending on the context (weak recommendation, low quality of evidence). In general, these techniques are useful for snoring in 80-90% of cases, but this decreases to 50% after the first year. As for the resolution of apnea, the success rate ranges from 40-50%, depending on the severity. Its indication depends on the anatomical examination, SAHS severity, age, the general state of the patient and his/her decision after having been properly informed. For now, palate implants have shown limited efficacy.<sup>55</sup>

### 6.3. Tongue base reduction surgery

The technique used can be laser or radiofrequency and, depending on the experience of the surgeon, success rates of up to 40% can be reached in cases of mild or mild-moderate SAHS (weak recommendation, low quality of evidence). Its indication should be submitted to the same conditions as in the former instance.

### 6.4. Multi-level surgery or Stanford phase (maxilomandibular)

(Weak recommendation, moderate quality of evidence). These are generally very invasive surgical techniques that should be preceded by a very precise anatomical study. Although in expert hands they may be effective,<sup>56</sup> at the moment in our setting these are reserved for cases of failed nasal CPAP or patients who had refused CPAP from the start, as high success rates have not been reproduced.

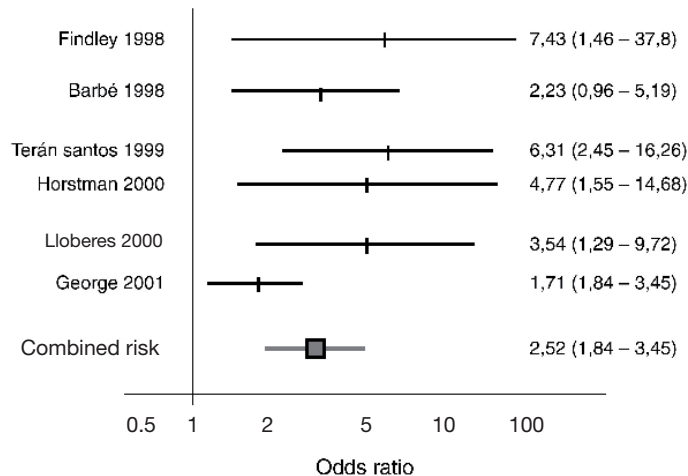
## SAHS in Children

SAHS in children is defined as a breathing disorder during sleep characterized by partial or complete obstruction of the upper airway (obstructive apnea) that alters normal ventilation during sleep and sleep patterns. It is associated with symptoms that include frequent nighttime snoring, sleep difficulties and/or behavioral problems.<sup>57</sup>

### Prevalence

The prevalence of SAHS in children aged 4-5 is estimated to be between 0.2% and 4.1% with a peak maximal incidence between the ages of 2 to 6<sup>58</sup> (high quality of evidence). The most

## Accident risk in SAHS patients

**Figure 7.** Accident risk of SAHS patients.

frequent cause of SAHS in childhood is adenotonsillar hypertrophy<sup>57</sup> (high quality of evidence), but the pathogeny of SAHS in children is a dynamic process and is the conjunction of anatomic and functional factors that lead to an imbalance and collapse of the UA.

### Symptoms and Morbidity

The clinical manifestations of SAHS in children are shown in table 7. The immediate consequences of the obstruction of the UA during sleep are: increased respiratory effort, intermittent hypoxemia, sleep fragmentation and alveolar hypoventilation, which can lead to delayed growth and development, pulmonary hypertension and *cor pulmonale*, systemic arterial hypertension, alterations in learning and behavior,<sup>57</sup> and, in cases of obesity, the association with metabolic syndrome (high quality of evidence).

### Diagnosis

The diagnostic method of choice for SAHS in children is PSG.<sup>2,57,59,60</sup> The coding of PSG in children differs from adults and criteria of the AASM are used<sup>59</sup> (high quality of evidence). Based on current knowledge, the DCNSAHS of the GES accepts an index of obstructive apnea between 1 and 3 as a cut-point for normality.<sup>2</sup>

RP with cardiorespiratory variable tracings is currently being studied<sup>59,61</sup> (weak recommendation, moderate quality of evidence). These guidelines recognize the diagnostic utility of RP, as long as it is used in accredited Sleep Units and with polygraphs validated in children (fig. 6).

### Treatment

The treatment of choice for SAHS in children is adenotonsillectomy,<sup>2,57,62,63</sup> whose efficacy is 78% (consistent recommendation, moderate quality of evidence). CPAP is the second line of treatment in SAHS in children,<sup>57,63</sup> in cases of impossible surgical treatment, given the persistence of SAHS after adenotonsillectomy and in some cases of children with obesity, craniofacial alterations or neuromuscular diseases (weak recommendation, moderate quality of evidence). Health

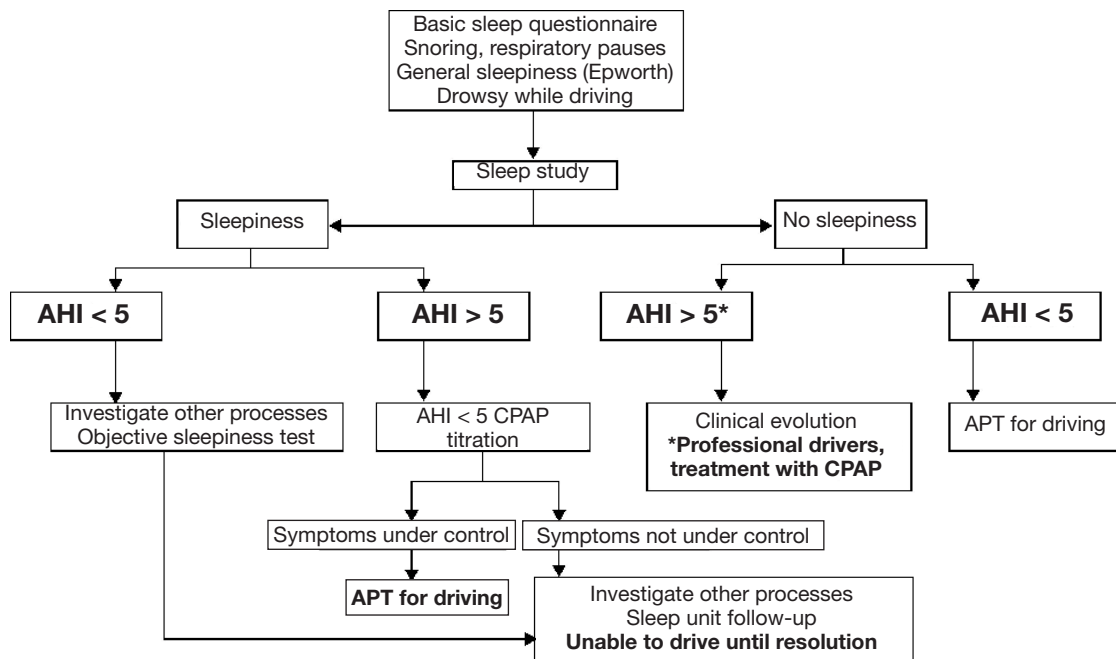


Figure 8. Strategy proposed for SAHS and vehicle operation.

education in dietary habits and sleep hygiene as well as orthodontic evaluation should be the norm in all children with SAHS.

For the diagnosis of SAHS in children, it is essential to have a high level of clinical suspicion in the General Pediatrics attention services.

### SAHS and Accident Risk

Traffic accidents are an important cause of death in the western world, and different estimates suggest that between 1 and 20% are related with excessive sleepiness. Within sleep disorders, SAHS deserves special attention, and its relationship with the production of accidents has been analyzed extensively in the medical literature.

The excess risk in drivers, be they professional or unprofessional, shows an odds ratio from 1.3 to 13, with a mean of 3.1 (fig. 7), taking into account the different designs, selection criteria and results measured (high quality of evidence).<sup>65-67</sup> When studies found in the literature analyze the risk factors that increase the probability of accidents in people with SAHS, most of the studies demonstrate that the more serious the symptoms as measured by AHI, the greater the risk for accidents (high quality of evidence).<sup>68</sup>

Nevertheless, daytime sleepiness, a symptom shown to be associated with SAHS, measured by tests that are either subjective (questionnaires) or objective (sleep latencies, etc.), is not solidly related with the appearance of traffic accidents, while drowsiness while driving is (medium quality of evidence).<sup>67</sup>

Studies involving professional drivers, in whom SAHS seems to be more prevalent (possibly due to the relationship between obesity and a sedentary lifestyle), do not indicate in any way that professional drivers have greater risk, as analyzed by kilometers driven/year.<sup>69</sup>

CPAP treatment reduces the percentage of accidents to that of the levels found in the general population (high quality of evidence).<sup>69</sup> Thus, CPAP treatment is cost-effective and Sassani et

al.<sup>70</sup> estimated 800,000 collisions avoided due to sleep apnea, with a savings of approximately \$11 billion and 980 lives annually in the United States.

It is difficult for physicians to evaluate the risk and the capacity to drive of sleep apnea patients, but it is essential to evaluate in each patient the risk when driving and warn them of the need not to drive if they feel sleepy. In Spain, detecting drivers at risk is the responsibility of the driver examination centers, based on the annex IV of the R.D. 772/1997, which typifies SAHS in section 7.2 within the group of respiratory-origin sleep disorders. It establishes that drivers with SAHS cannot obtain or renew their license without a previous report from a Sleep Unit, with a validity of two years for non-professional drivers and for 1 year for professionals.<sup>71,72</sup>

SEPAR urges the establishment of a European directive regarding causes of excessive daytime sleepiness and to establish regulations regarding SAHS as a limiting factor for obtaining drivers' licenses<sup>73</sup> (fig. 8).

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