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Review Article

The role of home sleep testing for evaluation of patients with excessive daytime sleepiness: focus on obstructive sleep apnea and narcolepsy

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ABSTRACT

Excessive daytime sleepiness (EDS) is a common complaint in the general population, which may be associated with a wide range of sleep disorders and other medical conditions. Narcolepsy is a sleep disorder characterized primarily by EDS, which involves a substantial burden of illness but is often overlooked or misdiagnosed. In addition to identifying low cerebrospinal fluid (CSF) hypocretin (orexin) levels, evaluation for narcolepsy requires in-laboratory polysomnography (PSG). Polysomnography is the gold standard for diagnosis of obstructive sleep apnea (OSA) as well as other sleep disorders. However, the use of home sleep apnea testing (HSAT) to screen for OSA in adults with EDS has increased greatly based on its lower cost, lower technical complexity, and greater convenience, versus PSG. The most commonly used, types 3 and 4, portable monitors for HSAT lack capability for electroencephalogram recording, which is necessary for the diagnosis of narcolepsy and other sleep disorders and is provided by PSG. These limitations, combined with the increased use of HSAT for evaluation of EDS, may further exacerbate the underrecognition of narcolepsy and other hypersomnias, either as primary or comorbid disorders with OSA.

Adherence to expert consensus guidelines for use of HSAT is essential. Differential clinical characteristics of patients with narcolepsy and OSA may help guide correct diagnosis. Continued EDS in patients diagnosed and treated for OSA may indicate comorbid narcolepsy or another sleep disorder. Although HSAT may diagnose OSA in appropriately selected patients, it cannot rule out or diagnose narcolepsy. Therefore, at present, PSG and MSLT remain the cornerstone for narcolepsy diagnosis.

1. Introduction

Excessive daytime sleepiness (EDS) is a common complaint in the general population and is associated with a wide range of sleep disorders and other medical conditions [1–4]. The prevalence of EDS, regardless of etiology, has been difficult to determine due to various methodologies used and differences in populations studied, with most estimates ranging from approximately 9%–28% [1]. Large recent survey studies in Western populations have reported EDS rates in the range of 12%–20% [5–7], while a longitudinal study that used a validated scale (mailed to respondents) to determine EDS reported a prevalence of 33% in Canadian respondents [1]. EDS is recognized as a significant public health problem due to its association with increased risk of motor vehicle and workplace accidents, as well as adverse impacts on productivity and quality of life (QOL) [8–11].

EDS, or hypersomnia, is characterized as the propensity to fall asleep during daytime hours, especially in passive and sedentary situations, and to suffer sleep attacks and take involuntary naps, with the inability to stay awake when alertness is required [11,12]. Potential causes of EDS have traditionally been divided in sleep medicine into three broad categories: (1) sleep deprivation/insufficient sleep, including such etiologies as insomnia, poor sleep hygiene/behavioral issues, jet lag, sleep phase delay, or shift work

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sleep disorder; (2) fragmented sleep, encompassing disruptive problems such as sleep breathing disorders (eg, snoring and sleep apnea), movement disorders (eg, restless legs syndrome), nightmares and parasomnias, epilepsy, and gastroesophageal reflux; and (3) increased need of sleep or primary hypersomnias, which include narcolepsy and idiopathic hypersomnias, among other etiologies [2,13,14]. Beyond these categories, other causes of EDS may include systemic diseases, psychiatric conditions, and adverse effects of medications (Table 1) [2]. Notably, while diverse conditions may include EDS as a symptom, the International Classification of Sleep Disorders-3 (ICSD3) lists only eight sleep disorders that require EDS for diagnosis [12,15].

Given the broad range of etiologic possibilities that EDS presents, evaluation of this symptom requires a careful and extensive physical and history as well as appropriate testing [2,13,16].

2. The advent of home sleep testing

Traditionally, laboratory polysomnography (PSG) has been the gold standard diagnostic procedure in sleep medicine [15,17]. Currently, however, most PSGs performed during nocturnal sleep serve to diagnose sleep-related breathing disorders, because of their relatively high and increasing prevalence, affecting an estimated 14% of men and 5% of women in the United States (US) [18]. The consequent economic burden and limited access to PSG led to the development of less costly procedures with wider access. Thus, home sleep apnea testing (HSAT) evolved and its use for patients with suspected obstructive sleep apnea (OSA), which may be the most common cause of EDS seen in clinical practice [2], became increasingly more widespread [19–21]. Other factors underlying the increased use of HSAT (also referred to as unattended portable monitors [PMs] or out-of-center testing) for OSA screening include fewer technical requirements such as the need for an in-laboratory attendant, and greater convenience, accessibility, and comfort for the patient. PSG requires an attendant and therefore an in-laboratory (or facility) overnight stay [19–21]. Clinical studies indicate that HSAT when used in uncomplicated patients with a high probability of moderate to severe OSA may provide similar diagnostic accuracy as PSG for moderate and severe OSA [22,23]. Third-party payers in the United States, including Medicare/Medicaid, accept HSAT diagnostic findings for payment of continuous positive airway pressure (CPAP) treatment for OSA [21,24,25]. These factors have also contributed to a decline in the number of PSG sleep centers, and of access to this service, parallel to the increase in use of HSAT [26,27].

However, use of HSAT has been highly controversial based on the substantial technical limitations, as compared with PSG, of the most commonly used Type-3 and -4 devices (Table 2) [28–32].

Studies and systematic review data indicate that Type-3 devices have false-negative rates for OSA of 13%–20%, with particularly poor detection of mild-to-moderate OSA [19,21,28,33,35,36]. Type-3 and -4 HSAT devices also lack the technical equipment, which is incorporated in PSG, to record sleep stages via electroencephalogram (EEG) (Table 2). This renders such devices incapable of detecting disturbances of sleep architecture such as sleep onset rapid eye movement periods (SOREMPs), which are key

Table 1
Common causes of excessive daytime sleepiness.

Sleep Disorders	
Sleep Deprivation/Insufficient Sleep	• Behavioral factors/poor sleep hygiene • Circadian rhythm sleep disorders (eg, shift-work sleep disorder, jet lag, delayed sleep phase, advanced sleep phase) • Insomnia
Fragmented/Disturbed Sleep	• Sleep breathing disorders (eg, OSA, snoring) • Movement disorders (RLS, PLMD) • Nightmares and parasomnias • Epilepsy • Gastroesophageal reflux
Primary Hypersomnias	• Narcolepsy (with and without cataplexy) • Idiopathic hypersomnias • Parasomnias • Kleine-Levin syndrome
Other Causes/Contributors	
Neurologic Conditions	• Parkinson's disease, other neurodegenerative disorders • Multiple sclerosis • Stroke • Epilepsy • CNS tumors • Structural brain disorder
Psychiatric	• Depression, other mood disorders • Anxiety • Schizophrenia, psychosis • Post-traumatic stress disorder
Organic diseases	• Heart failure • Chronic renal failure • Liver failure • Cancer • Obesity, hypoventilation syndrome
Medications	• Benzodiazepines • Barbiturates • Alcohol • Gamma-hydroxybutyric acid • Opiates • Anti-epileptics • Stimulant withdrawal

CNS, central nervous system; OSA, obstructive sleep apnea; PLMD, periodic limb movement disorders; RLS, restless legs syndrome.
Adapted from Slater et al., 2012 [2].

Table 2
AASM classifications for types of home sleep apnea testing devices.

Type	Portability	Channels, n	Signals	≥2 Airflow/ Effort Channels?	Identifies Sleep/ Wake States?	Measures AHI?
I	Facility-based (full, attended PSG)	14–16	EEG, EOG, EMG, ECG/HR, airflow, effort SaO_2	Yes	Yes	Yes
II	Portable (out-of-center, unattended PSG)	≥7	EEG, EOG, EMG, ECG/HR, airflow, effort SaO_2	Yes	Yes	Yes
III	Portable	≥4	Airflow and/or effort, ECG/HR, SaO_2	Yes	No	No, but estimates AHI[a]
IV	Portable	1–3[b]	All monitors that do not fit into Type-3 classification	No	No[c]	No, but estimates AHI[a]

AASM, American Academy of Sleep Medicine; AHI, apnea-hypopnea index; ECG, electrocardiography; EEG, electroencephalography; EMG, electromyography; EOG, electrooculography; HR, heart rate; PSG, polysomnography; SaO_2, arterial oxygen saturation.
[a] Both Type-3 and Type-4 monitors estimate the apnea-hypopnea index (AHI) by measuring the total number of episodes of apnea and hypopnea divided by the number of recording hours/time (as opposed to number of hours of sleep determined by EEG). Some Type-4 devices estimate sleep and wake states by peripheral arterial tone and estimate the AHI from the estimated sleep time.
[b] May have >3 channels provided that criteria for Type-3 monitors are not met.
[c] May include monitors that measure signals that are, in principle, able to identify arousals from sleep.
Adapted from Refs. [33,34].

components of the diagnosis of narcolepsy and other hypersomnias [19,20,28]. Hence, Type-3 and -4 devices are at present also incapable of contributing to diagnosis of multiple neurologic sleep disorders that may be comorbid with OSA, or present as the primary cause of EDS in a patient with suspected but unconfirmed OSA. In addition, perhaps a third of patients with OSA experience respiratory disturbances during rapid eye movement (REM) sleep, as determined with PSG, and REM OSA is independently associated with increased risks, versus nonREM (NREM) OSA, of hypertension, insulin resistance, and impaired human spatial navigational memory [37]. Discrete periods of abnormal breathing detected early in the study may suggest an early REM latency, although the clinical utility of this finding has not been systematically studied or validated. Therefore, the ability to detect sleep stages is also needed for assessment of a potentially high-risk sub-type of OSA. Respiratory inductance plethysmography has demonstrated utility as an adjunctive device in detection of REM sleep during PSG [38], and it is possible a comparable technique such as effort belts could help detect REM sleep; however, such approaches have not, to our knowledge, been studied.

While the advantages and disadvantages of HSAT for OSA diagnosis have been extensively debated and reviewed [28–32,34,39], there has been relatively little discussion of how its increased use may impact diagnosis of sleep disorders in general [40–42]. Among the conditions most closely associated with EDS, narcolepsy has been described as a “quintessential sleep disorder” whose understanding is likely to yield profound insights into the science of sleep [43]. Most sleep specialists have some level of expertise utilizing sleep studies for diagnostic purposes. Therefore, a detailed examination of the different requirements for diagnosis of narcolepsy and OSA, and comparison of the clinical profiles of patients with each disorder, may serve as an illustrative example of the limitations and proper utilization of HSAT when evaluating the patient with EDS.

3. Narcolepsy diagnosis

Narcolepsy is a neurologic disorder that causes profound EDS in all patients [15], affects an estimated 0.025%–0.05% of the general population in the US and Western Europe [44], and may significantly impair QOL if not treated effectively [45,46]. It is diagnosed as either narcolepsy type 1 (NT1) or narcolepsy type 2 (NT2) [15]. NT1 symptoms include EDS, cataplexy, sleep paralysis, hypnagogic/hypnopompic hallucinations, and disrupted nighttime sleep [15]. These together are considered the “classic” presentation of narcolepsy [47]. NT2 is defined as narcolepsy without cataplexy, but may include all other symptoms [15]. The symptoms of cataplexy, sleep paralysis, and hypnogogic/hypnopompic hallucinations have been posited as inappropriate intrusion of REM sleep into the waking state [48]. Accordingly, the diagnosis of narcolepsy requires clinical evaluation, PSG, and Multiple Sleep Latency Testing (MSLT) as an objective measure of sleepiness and REM sleep pressure (Table 3) [48]. In addition, any form of sleep testing must be able to demonstrate normal sleep sufficiently so that evaluation of EDS and REM sleep disturbances is possible, and to rule out other possible sleep disorders producing EDS.

Although narcolepsy and OSA may share the primary clinical symptom of EDS [15,49], EDS presence is universal in narcolepsy and required for diagnosis [50]. Alternately, not all patients with OSA report EDS [50]. As shown in Table 3, based on guidelines set forth in the third edition of the ICSD-3, NT1 is defined as EDS persisting for ≥ 3 months with sleep studies indicating an average sleep-onset latency ≤ 8 min on the MSLT following a nocturnal PSG negative for any comorbid sleep disorders, and two or more sleep-onset rapid eye movement periods on the MSLT (one of which may come from the preceding nocturnal PSG) with clearly documented cataplexy or low or absent levels of hypocretin/orexin (peptide neurotransmitters that regulate wakefulness, arousal, and REM and non-REM sleep states) in cerebrospinal fluid (CSF) along with sleep studies indicating disturbances [15]. Because cataplexy is absent in NT2, diagnosis of NT2 is more difficult than NT1, relies heavily on nocturnal PSG and subsequent MSLT, and is more dependent on the presence of EDS, which may occur in a wide range of conditions, as noted above (Table 1).

Diagnostic criteria for NT2 proposed by the American Academy of Sleep Medicine (AASM) include EDS persisting for ≥3 months, positive PSG/MSLT results, and normal or mildly decreased CSF hypocretin/orexin levels [15]. Recent study data suggest the repeatability of positive MSLT results was 10–14 times greater in NT1 versus NT2, casting doubt on the reliability of this measure for NT2, although these data await confirmation [51]. Moreover, diagnosis of cataplexy, which is pathognomonic of NT1, may be difficult due to the patient's reluctance to report the symptoms because of embarrassment or misunderstanding of them (and their relation to EDS), the failure of physicians to inquire about such symptoms in patients presenting with EDS [42], and the potential for cataplexy mimics, such as syncope, epilepsy, hyperekplexia, drop attacks, and pseudocataplexy [52]. Therefore, any sleep studies used for the diagnosis of NT1 or NT2 must at minimum include electroencephalogram (EEG). However, the most commonly used and studied Type-3 and -4 HSAT devices lack channels for EEG monitoring and the ability to monitor sleep

Table 3
Diagnostic criteria for narcolepsy type 1 and type 2: International Classification of Sleep Disorders [15].

Narcolepsy Type 1
Alternate names: Hypocretin deficiency syndrome, narcolepsy-cataplexy, narcolepsy with cataplexy
Diagnostic criteria
- Criteria A and B must be met.

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.
B. The presence of one or both of the following:
(1) Cataplexy and a mean sleep latency of ≤8 min, and two or more sleep onset rapid eye movement periods (SOREMPs) on a Multiple Sleep Latency Test (MSLT) performed per standard techniques. A SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.
(2) Hypocretin-1 concentration in the cerebrospinal fluid (CSF) measured by immunoreactivity is either ≤ 110 pg/mL or less than one-third of mean values obtained in normal subjects with the same standardized assay.

Narcolepsy Type 2
Alternate name: Narcolepsy without cataplexy
Diagnostic criteria
- Criteria A through E must be met.

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.
B. A mean sleep latency of ≤8 min and two or more SOREMPs are found on the MSLT performed per standard techniques. A SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.
C. Cataplexy is absent.
D. Either CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration measured by immunoreactivity is either greater than 110 pg/mL *or* greater than one-third of mean values obtained in normal subjects with the same standardized assay.
E. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, OSA, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.

phases and arousals (Table 2) [19,23]. This is particularly concerning in light of the generally poor recognition of narcolepsy among clinicians, predating the current use of HSAT, with an estimated mean diagnostic delay of 15 years following onset of narcolepsy symptoms [53,54].

4. Patient selection for HSAT

In general, the lack of real-time monitoring and inability of Type-3 and -4 HSAT devices to identify sleep versus wake periods increase the risk of technical failures and diagnostic inaccuracy compared to PSG [17]. In a review of 26 HSAT validation studies, the AASM determined that HSAT was associated with significant potential for diagnostic misclassification as compared with PSG, although seven of the studies failed to find any adverse effects of diagnosis by HSAT on OSA management and outcomes [17].

Based on these and other data, AASM guidelines recommend PSG as the standard diagnostic test for OSA in adults with suspected OSA following a comprehensive sleep evaluation [17,55]. Use of HSAT is recommended as an alternative to PSG for diagnosis of OSA only in medically uncomplicated adult patients with a high pretest probability of moderate-to-severe OSA [17,55]. The AASM further recommends that because HSAT is less sensitive than PSG for detection of OSA, a negative HSAT should be followed by a PSG in lieu of a second HSAT, and that the benefits of HSAT for patients depended on appropriate patient selection and diagnostic follow up as recommended in the guidelines. In a position statement, the AASM further clarified that the need for HSAT in appropriate adults should be determined by a physician, based on the patient's medical history and in-person examination; that HSAT should not be used for general screening of asymptomatic populations; and that raw data produced by automatic scoring of HSAT results should not be used for diagnosis and treatment decisions, but require interpretation by a physician who is board-certified in sleep medicine, or is under the supervision of one [56]. The AASM also does not recommend use of an HSAT for diagnosis of OSA in children (birth to 18 years of age), based on the lack of clinical trial data supporting this practice [57].

"Medically uncomplicated" adult patients are defined as those with an absence of conditions associated with increased risk of non-obstructive sleep-disordered breathing (SDB), including significant cardiopulmonary disease, potential respiratory muscle weakness due to neuromuscular conditions, history of stroke, or chronic opioid use, and no potential indications of a significant central sleep disorder, such as central sleep apnea, parasomnia, narcolepsy, or severe insomnia [17]. A high pretest probability of moderate-to-severe OSA is defined as EDS occurring on most days and presence of at least two of the following three criteria: (1) habitual loud snoring; (2) witnessed apnea or gasping, or choking; or (3) diagnosed hypertension [17]. The AASM guidelines further state that PSG should be used for evaluation of OSA in patients with the above-listed complications, and that negative, inconclusive, or technically inadequate HSAT tests should prompt an in-laboratory PSG [17,55]. Consideration of a second PSG is recommended if the initial PSG is negative and clinical suspicion for OSA remains [17].

These guidelines were supported by data from a meta-analysis of clinical studies using Type-3 HSAT devices, which concluded that these tests should be used only in adult patients with "high pretest probability of moderate-to-severe OSA and no unstable comorbidities" [23]. In addition, a retrospective analysis of the clinical characteristics of 193,221 patients referred for HSAT across North America between 2009 and 2013, and their HSAT outcomes, found that almost 90% were appropriately at high pre-test risk for OSA [58].

However, several real-world factors must be considered with regard to HSAT testing and its potential impact on detection and diagnosis of narcolepsy. Insurance company reimbursement policies are not perfectly aligned with the AASM guidelines and may allow for HSAT use for inappropriate patients without pre-authorization, while pre-authorization is required for PSG in patients recommended for it under AASM guidelines [27,59–62]. Many clinicians who refer for PSG or HSAT sleep testing are not sleep specialists and may have difficulty navigating the requirements for preauthorization [27]. In addition, while the AASM guidelines suggest criteria for a high pre-test probability of moderate-to-severe OSA, this condition is difficult to detect and assess because the key apnea symptoms occur during sleep, and pre-test clinical assessment has limited efficacy in detecting OSA [27,63,64]. One study reported sensitivity and specificity rates of 50%–60% and 63%–70%, respectively, for OSA diagnosis based on clinical impression alone [64]. Systematic review data have also found that none of the validated clinical screening instruments for diagnosis of OSA, such as the Berlin Questionnaire and Multivariable Apnea Prediction, have demonstrated reliable sensitivity and

specificity [33,65]. Therefore, it is unclear how accurately clinicians can and will determine high pre-test probability of moderate-to-severe OSA; this leaves open the possibility that some patients will be inappropriately referred for HSAT, perhaps based on the presence of EDS as a primary symptom.

Fig. 1 presents a suggested clinical algorithm for evaluation of patients with EDS and suspected narcolepsy, OSA, or both. In this process, the differing clinical profiles associated with narcolepsy and OSA may help guide correct diagnosis.

5. Narcolepsy and OSA: distinct clinical profiles

Given the highly specific, recommended criteria for the use of HSAT, recognition of the clinical profiles of OSA versus narcolepsy is essential to the selection of patients for HSAT and for correct diagnosis of each condition. Some of the key epidemiological and clinical characteristics of each disorder are shown in Table 4.

A major difference between the two disorders is the typical age range for onset of symptoms, which for narcolepsy occurs before the age of 20 in at least half of patients, and most commonly during adolescence (10–19 years old) [68,71,86–88]. OSA, by contrast, occurs most commonly in middle-aged and older adults [72,83]; as noted above, the AASM recommends use of HSAT in adult patients only, based on the lack of data for its use in pediatric patients [17,55,57]. However, because narcolepsy diagnosis is delayed by a mean of approximately 15 years, and up to several decades for some individuals, many middle-aged adults may present with EDS associated with narcolepsy that has been present but undiagnosed since their childhood [53,54,89]. OSA is also common in children, ranging in prevalence from 1% to 4% in pediatric populations, and is often associated with enlarged tonsils and adenoids [90,91].

The study described above in 193,221 patients referred for HSAT evaluation of OSA in North America between 2009 and 2013 reported that the majority of patients were men (59%) and middle aged, with a mean age of approximately 53 ± 14 years in both men and women [58]. Neck circumference was large in both men (16.9 ± 2 inches) and women (15.0 ± 1.3 inches), 47% of all patients had hypertension, 25.4% reported depression, and 17.4%, 16.6%, and 13.3% reported insomnia, diabetes, and heart disease, respectively; 11.4% of patients had restless legs syndrome. The Epworth Sleepiness Scale (ESS) score, a major measure of EDS, was 8.7 ± 5.3 in men and 8.6 ± 5.3 in women, indicating only mild EDS [58,92].

5.1. Differences in EDS between narcolepsy and OSA patients

Other large studies of patients diagnosed with OSA have reported mean ESS scores ranging from approximately 6 to 16, with scores positively correlated with presence and severity of patient-reported EDS at initial presentation [67,69,70]. In contrast, two large studies in patients with narcolepsy (n = 1099 [54] and n = 100 [68]), predominantly NT1, each reported a median ESS score of 18, with scores ranging from 10 to 24 in one study [68]. The initial study of the ESS, among patients seen at the Epworth Sleep Disorders Unit, found that mean (SD) ESS scores for patients eventually

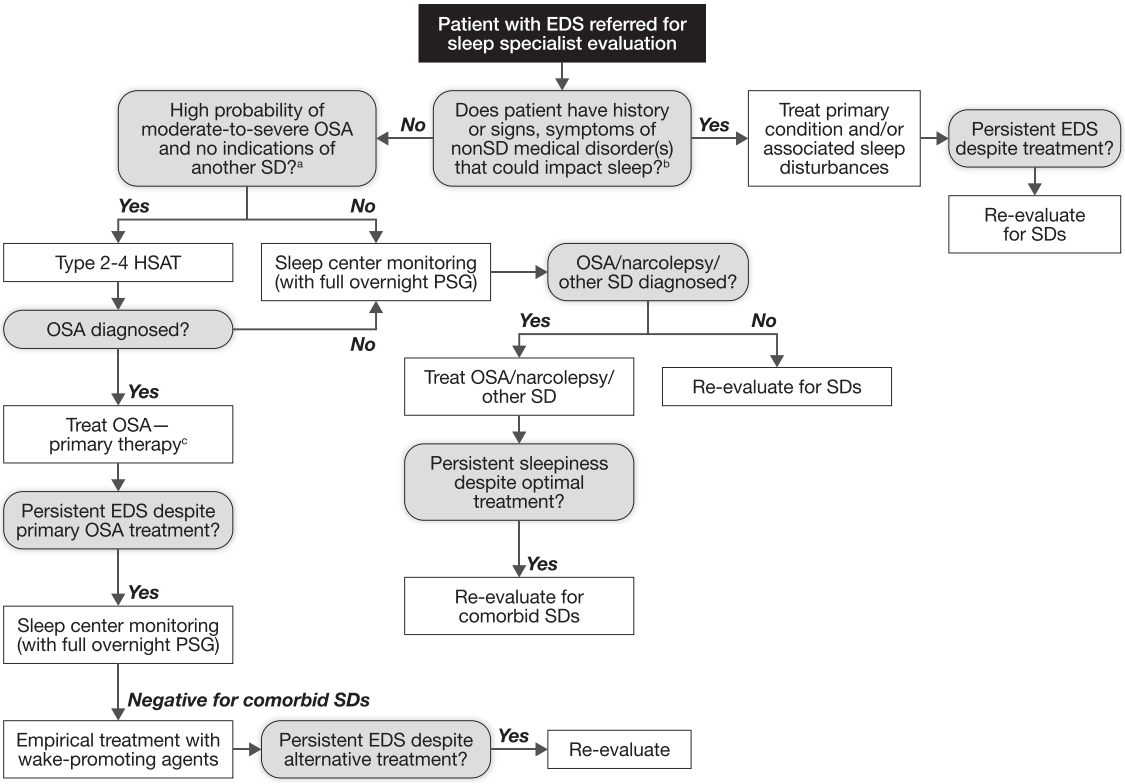

Fig. 1. Suggested clinical algorithm for diagnosis of suspected OSA, narcolepsy, or other sleep disorders based on symptoms of excessive daytime sleepiness. [a]A high pretest probability of moderate-to-severe OSA is defined as EDS occurring on most days and presence of at least two of the following three criteria: (1) habitual loud snoring; (2) witnessed apnea or gasping, or choking; or (3) diagnosed hypertension; [b]Conditions associated with increased risk of nonobstructive sleep-disordered breathing, including significant cardiopulmonary disease, potential respiratory muscle weakness due to neuromuscular conditions, history of stroke, or chronic opioid use, and presenting no potential indications of a significant sleep disorder other than OSA, such as central sleep apnea, parasomnia, narcolepsy, or severe insomnia; [c]For adults, primary OSA therapies include continuous positive airway pressure, behavioral therapies, adjunctive oral appliances, surgery, implantable stimulation devices. EDS, excessive daytime sleepiness; HSAT, home sleep apnea testing; OSA, obstructive sleep apnea; PSG, polysomnogram; SD, sleep disorder. Adapted with permission from Refs. [1,16].

Table 4
Epidemiological and clinical characteristics of narcolepsy and obstructive sleep apnea (OSA).

Characteristic[a]	Narcolepsy	OSA
Prevalence	0.03%–0.05% of general population [44]	14% of men, 5% of women[b] [18]
Percent patients with self-reported EDS at initial presentation	100% (required for diagnosis) [15]	15%–45%, depending on severity and age [49,50,66,67]
Range of ESS scores	10–24 [54,68]	6–16 [67,69,70]
Age of symptom onset, y	Median 23 years, occurring most commonly in teenage years, with peaks at 15 and 35 years of age [54,71]	Middle age (35–40 years) and prevalence increasing with age, with a 2–3 times higher prevalence in older persons (aged ≥ 65) versus those aged 30–64 years, plateauing at ~ 65 years [72]
Sex distribution	Slight preponderance of males over females [73]	2:1 male to female ratio [50]
Most common symptoms	EDS, cataplexy, sleep paralysis, hypnagogic/hypnopompic hallucinations, disturbed nocturnal sleep [15]	Witnessed apneas, snoring, gasping/choking at night, EDS, nonrefreshing sleep, fragmented sleep, morning headaches, insomnia [74,75]
Major risk factors	Human leukocyte antigen *HLA-DQB1*06:02* genotype; speculated risks include seasonal *Streptococcus* infections, H1N1 influenza, H1N1 vaccination, and childhood obesity [47,76]	Obesity (BMI > 35), aging, male sex, menopause, structural craniofacial and upper airway abnormalities, type 2 diabetes, congestive heart failure, atrial fibrillation, treatment-refractory hypertension [72,75]
Common comorbidities	Other sleep disorders, including OSA, RBD, PLMD, and RLS; diabetes; obesity; anxiety and mood disorders; COPD; ADHD; arthritis; lower back pain [42,68,76–80]	Obesity, diabetes, hypertension, coronary artery disease, myocardial infarction, congestive heart failure, stroke, chronic kidney disease, and other sleep disorders, including PLMD [72,75,81,82]

ADHD, attention deficit hyperactivity disorder; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea; PLMD, periodic limb movement disorder; RBD, rapid eye movement behavior disorder; RLS, restless legs syndrome.
[a] All values given are approximate, based on published clinical research.
[b] The frequency and magnitude of OSA risk factors may differ in men and women [see Refs. [58,83–85]].

diagnosed with OSA (n = 55) and those with narcolepsy (n = 13) were 11.7 (4.6) versus 17.5 (3.5), respectively [92]. Another study that compared clinical characteristics in patients with narcolepsy and with untreated OSA and CPAP-treated OSA (10 patients in each group) found that the mean (SD) ESS score in the narcolepsy patients was 19 (4.1) versus 14.8 (4.4) in untreated OSA patients and 6.9 (3.6) in CPAP-treated OSA patients [93]. Mean (SD) body mass index (BMI) was elevated (in obese range) and similar in all three groups (30.9 [5.9], 32.4 [4.0], and 31.5 [4.1] in narcolepsy, untreated OSA, and treated OSA, respectively).

The prevalence of EDS also differs between OSA and narcolepsy. While EDS is virtually universal in narcolepsy and is required for its diagnosis [15], reported rates of patients with EDS at initial presentation who were subsequently diagnosed with OSA have ranged widely, from 15% to 45%, with higher rates associated with greater severity of OSA and older age (Table 4) [49,50,66,67,94]. In addition, study data on the correlation of subjective EDS, as measured with the ESS, with OSA have been mixed. Some large studies in OSA populations have reported a strong positive association of ESS scores with apnea-hypopnea index (AHI) or respiratory disturbance index (RDI), as well as other factors including hypochondriasis, depression, diabetes, BMI, and oxygen desaturation index [94–97]. However, other studies have reported low sensitivity and poor predictive ability of the ESS when used for screening for OSA [98–100]. Still more studies have reported either lack of a significant relationship of ESS with AHI and other measures of SDB [98,101,102], or a weaker relationship of ESS scores to OSA than with other factors such as depression, BMI, or aging [3].

5.2. EDS and OSA in women

The relationship between subjective EDS and OSA appears to be particularly questionable in women [83,102]. Indeed, multiple sex differences in OSA symptoms and manifestations have been reported, including a weaker relationship of self-reported sleepiness to ESS scores > 10; more frequent complaints of fatigue, morning headaches, insomnia, depression, nightmares, and hallucinations; and more frequent awakenings but fewer breathing pauses, in women compared with men [84,85]. A general population study in 400 women, with oversampling of habitually snoring individuals, found that EDS in these subjects was independent of the AHI, although it was associated with habitual snoring as well as age, obesity, smoking, and other sleep parameters [102]. An analysis of the sex differences in predictors of OSA diagnosed via HSAT (n = 272,705) found that EDS (ESS ≥ 10) contributed no unique variance in OSA in adjusted models for either sex, although EDS was slightly more predictive of OSA in men than in women [83]. This study also found other differences in the predictive profiles for OSA in men versus women [83]. While advancing age was the strongest independent OSA predictor in both men and women, age > 45 years was more predictive for women than for men (Fig. 2).

In addition, some “classic” OSA symptoms such as witnessed apneas, visceral adiposity, and neck circumference were stronger predictors in men, while hypertension was a stronger predictor in women. Snoring and diabetes were equally predictive in men and women. Overall, based on the available data, researchers suggest that EDS alone is an unreliable basis for suspicion of OSA, and that alternative causes should be investigated such as aging, adiposity or obesity, hypertension, diabetes, renal disease, and other conditions that may be comorbid with OSA [50,83].

6. Comorbid narcolepsy and OSA

Studies have reported that approximately 20%–30% of patients diagnosed with narcolepsy have comorbid OSA, which is positively correlated with age and BMI, and is associated with male sex [42,68,103,104]. In a 15-year community study, subjects with narcolepsy (n = 68) had a 69.3-fold increased odds ratio for OSA at narcolepsy diagnosis versus healthy controls (n = 272), which diminished to 13.6-fold at the end of the study; other persisting comorbidities of narcolepsy over the study period included obesity, psychiatric disorders, endocrinopathies, and chronic low back pain [105]. A study in 133 sleep medicine clinic patients diagnosed with narcolepsy found that 33 (24.8%) had an AHI > 10 [42]. As shown in other populations, OSA in this cohort was associated with older age, higher BMI, and male sex. Of the 33 patients with OSA, 10 had been initially diagnosed with OSA only, while the diagnosis of narcolepsy, which occurred following evaluation for residual EDS despite CPAP therapy, was delayed by a mean of 6.1 ± 7.8 years. The other 23 patients had been diagnosed simultaneously with OSA and narcolepsy. Major factors in the delay of narcolepsy diagnosis included the failure of patients to spontaneously report cataplexy,

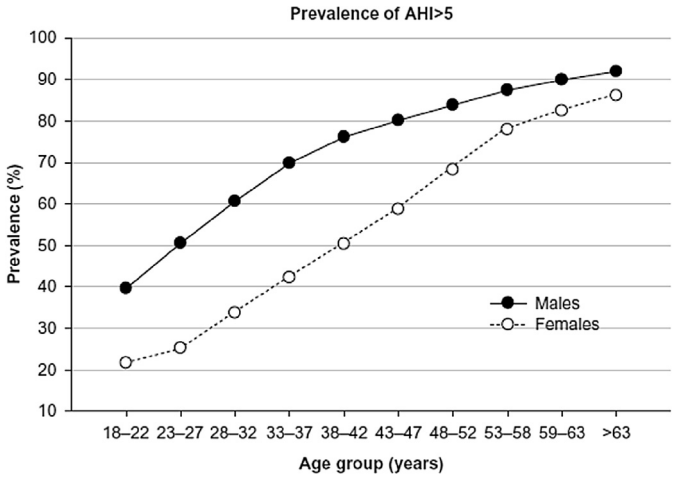

Fig. 2. Prevalence of apnea-hypopnea index >5 as derived from home sleep testing in men (n = 155,700) and women (n = 117,005) by age group in a North American population; retrospective analysis of sex differences. AHI, apnea-hypopnea index. Source: Reference [35]; reprinted with permission.

and failure of examining physicians to inquire about it. Of the 20 (60.6%) patients who initially received only CPAP treatment, only three (15%) reported improvement in EDS. Based on these limited data, the study authors suggested that narcolepsy may play a greater role in the pathophysiology and severity of EDS than OSA when the conditions are comorbid, although more studies are needed. The authors also commented that young age and severe EDS combined with a moderate AHI are factors that may support a suspicion of narcolepsy.

Few study data on the prevalence of comorbid narcolepsy in patients with a primary diagnosis of OSA are available. Persistent EDS despite CPAP treatment has been reported to occur in 12%–65% of patients with OSA, and has been investigated in multiple studies [70,106–109]. Narcolepsy is not among the risk factors for CPAP-resistant persistent sleepiness reported in the literature, which include higher baseline (pretreatment) ESS score and lower RDI, periodic limb movement, insufficient sleep syndrome, depression, diabetes, heart disease, and young age [107,109]. However, one study in 502 patients with OSA from 37 French sleep centers found that comorbid narcolepsy was present in 1 (2%) of the 60 patients from this sample who had CPAP-resistant persistent sleepiness, while narcolepsy was present in <1% of the remaining patients without persistent sleepiness [70]. Overall, there is little evidence to suggest that OSA is associated with an increased risk for narcolepsy, and vice versa.

7. Clinically distinguishing narcolepsy and OSA

In the case of a negative HSAT result for OSA in a patient judged to have high pretest probability of moderate-to-severe OSA, or of persistent sleepiness despite CPAP treatment in a patient diagnosed with OSA, evaluation for narcolepsy (alone or comorbid with OSA) may be indicated. Symptoms and clinical characteristics that particularly support suspicion of narcolepsy in such cases include: cataplexy (either reported by the patient or elicited by the physician); younger age; absence of cardiovascular disease; severe sleepiness (ie, ESS score > 16); and presence of other symptoms such as sleep paralysis, hypnagogic/hypnopompic hallucinations, or disturbed nocturnal sleep (Table 4). PSG with MSLT may be necessary to confirm the diagnosis [15]. Conversely, cases may arise of patients diagnosed with narcolepsy who report EDS despite adequate therapy, either from the beginning of treatment, or after years of successful therapy. For example, a patient who had been diagnosed with and treated effectively for narcolepsy during adolescence or young adulthood may eventually develop comorbid OSA associated with aging, weight gain, and other factors affecting sleep breathing, leading to residual EDS. Clinical factors that support suspicion of comorbid OSA in such a patient include witnessed apneas, snoring, and other symptoms of sleep breathing disorders; adult middle-age; BMI >35; male sex; menopause; structural craniofacial and upper airway abnormalities; and type 2 diabetes and cardiovascular disease (Table 4). PSG (Type 1 sleep study) is preferred for evaluation for comorbid OSA or other sleep disorders in the patient with treated narcolepsy and persistent EDS. However, if the clinical factors in a patient with narcolepsy indicate a high pretest probability of moderate-to-severe comorbid OSA, as per AASM guidelines, an HST may be appropriate.

8. New HSAT/Portable monitor devices

Looking toward the future, additional alternative methods for HSAT are being developed that may have greater utility than current devices for diagnosis of narcolepsy [110]. While current scalp electrodes used for EEGs are not practical for home application by patients, researchers have developed a disposable set of forehead electrodes for EEG and a supplementary set of chin electromyogram electrodes for sleep staging [111]. A study of the utility of this device in 31 adult volunteers found that there were no statistically significant differences in measurement of total sleep time (TST), sleep efficiencies, or sleep latency with the forehead and chin electrode sets versus standard PSG; however, the electrodes recorded significantly higher proportions of stages 1 and 2 sleep and lower percentages of stage 3 and REM sleep. Overall, sleep epoch-by-epoch agreement for the methods was approximately 80% [111]. Two wrist-worn devices were evaluated in 34 children (n = 17) and adolescents (n = 17) for recording sleep onset, offset, sleep intervals, actual sleep time, and wake after sleep onset, compared with PSG [112]. The study found that both devices demonstrated high sensitivity versus PSG (>0.91) in both younger children and adolescents, although specificity ranged from 0.58 to 0.77, based on device and age group.

A general approach being studied for HSAT is the use of cardiorespiratory signals for sleep stage classification. One research team has developed a contact-free monitoring system composed of an under-the-mattress piezoelectric sensor and smartphone application to record vital body signs and analyze sleep [113]. In a study comparing this system with PSG, data were collected for heart rate, respiratory rate, body movement, and sleep parameters as recorded with the portable monitoring system over one to three nights at home and compared with epoch-by-epoch data from a control group that underwent full PSG overnight in a laboratory [113]. The results showed similar times for TST, wake, and sleep phases, with a linear correlation for TST between the two systems of 0.98 (R = 0.87). Sensitivity, specificity, and accuracy were 92.5%, 80.4%, and 90.5% for the epoch-by-epoch comparison of the contact-free system with PSG. Another approach utilized recording of heart rate with a Holter monitor and of wrist movements with actigraphy [114]. A study of this system in 12 healthy volunteers found that recordings over 48 nights allowed for similar evaluation of sleep architecture and continuity compared with standard PSG, with correlations ranging from good to excellent [114]. Other researchers have shown that systems recording electrocardiogram signal data have demonstrated moderate accuracy versus PSG in distinguishing REM from NREM sleep [115,116].

A Canadian research team has developed an HSAT device specifically designed to diagnose narcolepsy via detection of SOREMPs, with EEG supported with feature extraction and binary

classification algorithms [117]. The sleep staging algorithms are based on several classification techniques including Learning Vector Quantization, Probabilistic Neural Network, and Feed-forward Neural Network, which together comprise a "support vector machine" (SVM). The classification accuracy of the SVM was found to be 96% when validated with jackknifing cross-validation statistical analysis, which included manual scoring of 60 recorded epochs by a physician. The authors further stated that their device could be used to log occurrences of narcoleptic symptoms throughout waking periods to aid the treating physician in management, and an alarm will sound for the patient and companions when such episodes occur. A mobile two-channel in-home EEG recording device demonstrated capability of displaying whole-night sleep in a spectral display that permitted assessment of general sleep stability, dominant frequencies, cycle lengths, stage lengths, and other sleep architecture data [118]. These researchers devised unique classifications for sleep stages based on the novel spectral data produced by their system. Smartphone applications may represent the most likely future technology for broad-based, low-cost sleep monitoring [119]. However, a review of 11 validation studies of such devices versus PSG found that more studies are needed to assess their reliability, particularly with regard to sleep-wake detection.

9. Conclusions

The increased use of HSAT devices and diminishing availability of PSG for evaluation of OSA may have repercussions in sleep medicine beyond OSA diagnosis. PSG is essential for diagnosis of narcolepsy. Therefore, the decreased use of PSG for suspected but unconfirmed OSA may risk failure to detect narcolepsy, either comorbid with OSA or another sleep disorder, or as the primary condition. In a patient with EDS, diagnosis of narcolepsy requires ruling out alternative causes of the EDS. Ideally after other, more common conditions (eg, OSA) are ruled out, the results of PSG and MSLT, including findings such as SOREMPs, may be used to diagnose narcolepsy, based on the established criteria. While a Type-3 or -4 HSAT, with or without sleep surrogates may be used to screen for OSA, these testing devices are not useful for evaluation or diagnosis of suspected narcolepsy. Moreover, as identified in the current AASM recommendations, HSAT cannot reliably be used to "rule out" OSA; as noted in these recommendations and reflected in the current practice of most sleep specialists, only attended PSG (Type 1 testing) can definitively rule out OSA and exclude or identify other sleep disorders.

As a separate issue, there are presently insufficient data to demonstrate that any HSAT device can reliably demonstrate "acceptable sleep," which is necessary for such testing to contribute to the diagnosis (as opposed to the exclusion) of narcolepsy. Therefore, despite the widespread use of HSAT for OSA screening, PSG determination of normal sleep structure, prior to daytime evaluation with careful review of clinical history, remains a cornerstone of practice for narcolepsy diagnosis. In patients diagnosed with OSA who remain hypersomnolent, a full evaluation for narcolepsy (PSG, MSLT, and clinical assessment) and other conditions should be performed.

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