



## A Case Based Approach to Evaluation and Management of Simple and Mixed Disorders of Sleep

Alexandre R Abreu and Alejandro D Chediak\*

Department of Medicine-Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, University of Miami Miller School of Medicine, USA

### Abstract

Sleep apnea is a common respiratory disorder of sleep which when untreated or inadequately treated has profound adverse effect on behavioral, metabolic and cardiovascular health outcomes. Breathing disturbances of sleep may be characterized as obstructive, central, mixed or a complex combination where both central and obstructive breathing disturbances of sleep coexist. In cases with high clinical index of suspicion for isolated moderate to severe obstructive sleep apnea, the diagnosis and optimal treatment can be delivered with a traditional laboratory approach or with domiciliary tools. However, many cases of sleep apnea are multifaceted or overlap with other disturbances of sleep, rendering such cases challenging to diagnose and manage thereby necessitating comprehensive assessment in an accredited sleep laboratory. Rather than treat individual disorders of sleep and breathing out of context with clinical practice, this manuscript aims to present real-life clinical cases that facilitate the discussion and education pertaining to the evaluation and management of selected disorders of sleep and breathing.

### Introduction

Sleep can be considered rapidly alternating, naturally occurring behavioral state where the brain dissociates from the environment. For many years, the principle medical concern pertaining to sleep was its absence, namely insomnia, and disorders of sleep were generally considered rare, infrequently studied and, therefore, poorly understood. The past several decades has seen an upsurge in sleep research with parallel growth in clinical sleep disorders as a unique discipline of medicine. The third edition of the International Classification of Sleep Disorders (ICSD-3) [1] describes over 90 distinct disorders of sleep and it is not uncommon for two or more distinct disorders of sleep to coexist in one subject [2].

The term Sleep Disordered Breathing (SDB) encompasses several respiratory disturbances of sleep including Obstructive Sleep Apnea (OSA), Central Sleep Apnea (CSA) and sleep-related hypoventilation syndromes. Of these, OSA is the most common with prevalence, in one population study, estimated to be 14% in men and 5% in women [3]. In selected populations, the prevalence of OSA can be considerably higher, approaching 80% and 70% in bariatric surgery and ischemic cerebrovascular disease populations, respectively [4,5]. OSA sufferers are often sleepy during the day, manifest cognitive impairment and are at increased risk for developing metabolic derangements, and cerebrovascular and cardiovascular disease including, coronary artery disease, difficult to control hypertension, arrhythmias and stroke [6-8]. Using cost data from the year prior to the diagnosis of SDB, Kapur [9] and colleagues reported a mean annual medical cost savings of \$1336 (49% reduction) per case compared to age and gender matched controls. Further, they estimate that in the United States, untreated sleep apnea may add \$3.4 billion in medical costs.

Diagnosing SDB requires the measurement of breathing during sleep. ICSD-3 defines OSA as a polysomnography (PSG) derived obstructive respiratory disturbance index (RDI)  $\geq 5$  events/hour associated with symptoms or an obstructive RDI  $\geq 15$ /hour in the absence of symptoms [1]. The RDI is derived by the sum of all apneas, hypopneas and respiratory effort related arousals (RERA) divided by the number of hours of sleep while the apnea hypopnea index (AHI) is similar with the exception of the exclusion of RERA events from the calculation. There is general consensus on the definition of apnea. However, the criteria for identifying hypopnea are not uniform [10]. Hypopnea can be scored if associated with either a cortical arousal in the sleep EEG or a non-artefactual decline in oxyhemoglobin saturation by 3% to 4%. In this manuscript, all case specific indices of breathing required a 4% decline in oxyhemoglobin saturation as prerequisite for identifying hypopnea.

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#### \*Correspondence:

Alejandro D Chediak, Department of Medicine-Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, University of Miami Miller School of Medicine, P.O. Box 016960 (D-60) Miami, Florida 33101, 305-243-9999, USA,

E-mail: Axc1599@med.miami.edu

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**Table 1:** Evidence based treatment options for adult CSA syndromes [40,41].

Primary CSA	Acetazolamide	
	Hypnotics (zolpidem and triazolam)	
	PAP therapies	
CSA due to HF (with and without CSB) after optimization of HF therapy	PAP	CPAP
		BPAP in spontaneous timed mode if no response to CPAP
		ASV only if preserved EF ( $\geq 45\%$ )
	Nocturnal oxygen	
CSA in end stage renal disease	CPAP	
	Bicarbonate buffer during dialysis	
	Nocturnal dialysis	

OSA is a potentially life-threatening disorder that may be comorbid with a secondary sleep disturbance or masquerade as another sleep disorder [2,11]. Therefore, it follows that, when OSA is suspected, a comprehensive sleep evaluation and appropriate diagnostic testing is necessary to address OSA along with any possible comorbid sleep disturbances. This narrative aims to highlight the evaluation and management of SDB with cases illustrative of uncomplicated isolated OSA and OSA complicated by another sleep disorder, specifically CSA and narcolepsy.

## Case 1

### History and clinical features

OS presented to the sleep specialist as a 55-year-old male with disruptive snoring, spouse observed apnea and Excessive Daytime Sleepiness (EDS). Onset and severity of symptoms correlated with a 50-pound weight increase over the preceding 2 years. Prior to the weight increase, he neither snored loudly nor complained of EDS. Hypersomnia was severe as evidenced by 2 episodes of unintended dozing while driving. The Epworth Sleepiness Scale score [12] was 12 in the light of 8 hours of reported sleep per night on workdays and 10 hours on days off. Increasing the opportunity for sleep at night and daytime sleep was not helpful at alleviating EDS.

Salient features on physical examination include a body mass index of 36.8 kg/m<sup>2</sup>, neck circumference of 17.5 inches, blood pressure 154/103 mmHg and oxyhemoglobin saturation of 97% while at rest and breathing room air. The oral pharyngeal aperture is Mallampati class 3 [13] with scalloping of the tongue, narrowing of the maxilla and marked enlargement of the uvula and soft palate. The maxillary overjet was 1 mm. The STOP BANG [14] score was 8, a value predictive of moderate to severe OSA. As the presentation was characteristic for OSA, a home sleep apnea test (HSAT) was deemed appropriate [15,16].

HSAT was performed with a device meeting criteria for a type III monitor [15]. The recording, consisting of 7 hours and 11 minutes of artifact free data, shows AHI of 40 and oxyhemoglobin saturation was below 90% during 9% of the recording. After a session of education and positive airway pressure (PAP) therapy mask fitting, Automatic Positive Airway Pressure (APAP) was prescribed.

On follow-up, 30 day mean daily utilization of positive airway pressure therapy was 6 hours and 39 minutes and APAP was used for 4 hours or more on 80% of days. The apnea plus hypopnea index (AHI) on APAP was 3.3 indicating optimal control of OSA [17]. APAP treatment of obstructive sleep apnea completely controlled disruptive snoring, spouse observed apnea and normalized diurnal

alertness. The 6-week posttreatment Epworth sleepiness scale score was 4 and systemic blood pressure had decreased to 140/87 mmHg without weight reduction or resorting to pharmaceutical intervention.

### Discussion

This case represents the characteristic presentation of a patient with increased risk of moderate to severe OSA in an individual without clinically relevant comorbid conditions that might otherwise degrade the accuracy of HSAT [15,16,18]. Among randomized control trials comparing an at home versus in laboratory paradigm that most closely approximates clinical circumstances for the diagnosis and treatment of OSA, the clinical definition of increased risk for moderate to severe OSA varies [19-22]. However, the 2017 clinical practice guideline for diagnostic testing for adult sleep apnea from the American Academy of Sleep Medicine (AASM) [16] promotes the notion that increased risk for moderate to severe OSA can be defined as EDS on most days plus the presence of at least 2 of the 3 following criteria: habitual loud snoring; witnessed apnea or gasping or choking; or diagnosed hypertension.

HSAT is less sensitive than PSG for detection of OSA. Employing Type 3 HSAT devices and using an AHI  $\geq 5$  cut off for diagnosing OSA, Kapur and company [16] calculated HSAT accuracy in a high risk population ranges from 84% to 91% whereas in a low risk population, accuracy ranges from 70% to 78%. Similar analysis using an AHI  $\geq 15$  and AHI  $\geq 30$  cut off in a high-risk population estimates accuracy of 65% to 91% and 88%, respectively. A false-negative HSAT can lead to significant harm. Considering the afore mentioned and given that repeat HSAT is unlikely to change diagnostic outcome, a single negative, inconclusive or technically inadequate HSAT should be followed by PSG.

Continuous positive airway pressure (CPAP) therapy after titration with attended PSG in the sleep laboratory has long been considered the standard of care for treating OSA. Technological advance has fostered PAP devices capable of assessing breathing patterns and responding to impending respiratory instability by modifying their output. Collectively known as APAP technology, these devices are purported to auto-adjust and control OSA thereby obviating the need for titration polysomnography. In properly selected patients treated by sleep experts, APAP titration yields treatment settings and clinical outcomes similar to that derived using CPAP with setting based on attended laboratory titration [19,21,22]. However, not all APAP devices sense or respond to breathing with similar algorithm and device accuracy should be considered device dependent. Outcomes of OSA treated with PAP have been shown to be superior when delivered by board-certified sleep specialist and/or

**Table 2:** Other therapeutic interventions for adult CSA [40,49,50].

Supplemental carbon dioxide
Increasing dead space
Theophylline
Transvenous phrenic nerve pacing
Overdrive atrial pacing
Expiratory nasal resistance
Positional therapy

in facilities accredited by the AASM [23-25]. It is, therefore, advisable for PAP management to be directed by the sleep specialist or through an AASM credential facility equipped with a PAP management program.

### Key learning points

1. OSA often occurs in the context of obesity and weight increase [26].
2. Inappropriately selected uncomplicated cases of OSA managed by a sleep specialist, HSAT can reliably diagnose OSA and produce outcomes similar to that using a paradigm that involves PSG for diagnosis and adjustment of PAP therapy [19,21,22,27].
3. APAP treatment of uncomplicated OSA is an acceptable alternative to CPAP and may obviate the need for CPAP titration PSG [18,19,21,22,28].
4. Treatment utilization by an objective means is an important outcome metric [29,30].
5. Follow up in a sleep specialty clinic with physician credentialing in sleep medicine and/or AASM facility credentialing may improve outcomes in OSA treated with PAP [23,25].

## Case 2

### History and clinical features

OF is a 69-year-old male referred to the sleep specialist in Miami, Florida by his cardiologist in the evaluation of suspected OSA. The syndrome was considered because of EDS (Epworth 14), loud snoring, hypertension and atrial fibrillation. Additionally, insomnia, described as hourly awaken to void his urinary bladder plus, about 3-4 times per week, prolonged awakenings after nocturia. Self-reported sleep duration was 6-9 hours on nights without prolonged awakenings and less than 4 hours on nights when nocturia was followed by prolonged awakening. His medical history was positive for hypertension, diabetes, chronic kidney disease and recent onset atrial fibrillation. OF has ceased smoking cigarettes at age 35 years, consumed only one decaffeinated coffee in the morning and less than 1 alcoholic beverage per month. Opiates were not being used. The family history was negative for disorders of sleep.

Salient features on physical examination include a BMI of 29.5 kg/m<sup>2</sup>. Neck circumference was 18.75 inches and the oral pharyngeal appearance is Mallampati class 3 with thick tongue, enlarged soft palate and a wide and slightly long uvula. Maxillary overjet is 0 mm - 1 mm. Examination of the heart was remarkable for irregular rhythm. The STOP BANG [14] score was 6, a value predictive of moderate to severe OSA. Recent onset atrial fibrillation, chronic kidney disease and insomnia prompted a recommendation for attended PSG over HSAT. PSG with both diagnostic and therapeutic components (split night) was ordered.

Split-night PSG confirmed sleep apnea with AHI 53.7 and RDI 54.4. However, central apnea index was 14 on the diagnostic portion of the PSG and on the therapeutic portion with application of CPAP, obstructive events were abolished but CSA persisted with central apnea index (CAI) of 60 on CPAP. Cardiac rhythm was atrial fibrillation. His final sleep diagnosis was severe obstructive and treatment emergent CSA. After confirmation of left ventricular ejection fraction > 45%, PSG for titration of adaptive servo ventilation (ASV) PAP technology was conducted. The ASV titration PSG confirmed optimal control of obstructive and central sleep apnea events.

Domiciliary treatment with ASV led to resolution of nocturia, prolonged awakenings and improvement in EDS (post treatment Epworth 2). On follow-up, 180 day mean daily utilization of positive airway pressure therapy was 5 hours and 42 minutes and APAP was used for 4 hours or more on 80% of days. The AHI on APAP was 0 indicating optimal control of OSA [17].

### Discussion

The patient has EDS, hypertension and loud snoring, clinical features consistent with increased risk for moderate to severe OSA as similarly described on the earlier case. However, the presence of clinically significant comorbid cardiovascular disease and insomnia render the case unsuitable for HSAT [15,16]. The presence of atrial fibrillation increases the probability for concomitant CSA [31], a respiratory arrhythmia where HSAT has not been suitably validated as a means to establish the diagnosis [16]. Hence, PSG is the appropriate diagnostic intervention. Indeed, had HSAT been conducted, he would have required attended PSG for confirmation of CSA.

ICDS-3 [1] identifies 8 distinct types of CSA syndromes of which 2 are unique to infancy and prematurity. CSA with Cheyne-Stokes breathing, CSA due to a medical disorder without Cheyne-Stokes breathing (CSB), CSA due to high-altitude, CSA due to medication or substance (i.e. opiates), primary CSA and treatment emergent CSA are the purported adult forms of CSA. In this instance, CSA with CSB, a form of crescendo decrescendo breathing most often seen in patients with systolic or diastolic heart failure, high altitude CSA, and medication related CSA can be excluded from the differential diagnosis. Treatment emergent CSA, primary CSA and CSA due to a medical disorder without CSB are the more likely CSA subtypes. CSA attributed to medical disorder without CSB often occurs in the context of severe neurologic disease with brainstem lesions, the breathing pattern can be ataxic, and afflicted individuals can have diurnal and/or nocturnal hypoventilation, features lacking in this case. Primary CSA patients have a higher incidence of atrial fibrillation, but so do patients with OSA, the latter as was diagnosed by PSG. Hence, CSA in this instance is most representative of treatment emergent CSA.

Some use the term "complex sleep apnea" to identify cases where OSA and CSA coexist. As used by some clinicians, the terminology makes no distinction of CSA causality and as such is inherently vague [32]. Nonetheless, the term continues to be used but with increasing frequency to describe CSA and OSA occurring in the context of PAP treatment of OSA [33,34]. The pathogenesis of treatment emergent CSA is not well understood and may involve dual effects of anatomic and physiologic vulnerability to OSA plus respiratory control instability with enhancement of loop gain [35]. Maladaptation to PAP with repeated arousals and sleep-onset central apneas and activation of the inspiratory inhibitory component of the Hering-Bruer reflex [36] are other proposed pathophysiologic mechanisms of treatment emergent CSA, the latter consistent with the clinical

**Table 3:** PSG and MSLT criteria for diagnosing narcolepsy<sup>1</sup>.

Mean sleep latency less than or equal to 8 min
To or more sleep onset REM periods (REM within 15 min. of sleep onset)
A sleep onset REM period on the preceding nocturnal PSG may replace 1 sleep onset REM period on the MSLT

<sup>1</sup>MSLT must follow PSG and be performed according to standardized techniques [45]

observation that treatment emergent CSA seems to be more common in patients requiring higher levels of PAP. To the extent that one or more of these mechanisms are involved in a given case is unknown. However, in this instance the presence of CSA prior to the application of CPAP suggests high loop gain was involved in the pathogenesis of his treatment emergent CSA.

Treatment emergent CSA occurs in approximately 6% - 10% of CPAP titration polysomnograms [37,38]. However, treatment emergent central sleep apnea can be transitory and resolve with 2-3 months of continued CPAP treatment in all but about 2% - 8% of cases [38,39].

The treatment of CSA syndromes in adults is based on the underlying mechanism [40]. The science to support specific therapies is limited and that which is available is based on case series, small randomized trials with surrogate endpoints and a handful of randomized controlled trials largely limited to patients with both OSA and CSA. Table 1 list the evidenced based CSA subtype specific therapeutic alternatives as advanced by the AASM in the 2012 and 2016 Practice Parameters for the treatment of central sleep apnea in adults [40,41]. In Table 2 we list other therapeutic interventions of reported benefit in the treatment of CSA.

### Key learning points

1. CSA can occur with and without with OSA.
2. The clinical circumstance when relevant numbers of central apnea coexist with obstructive apnea has been termed complex sleep apnea [34,38].
3. Complex sleep apnea at sea level is most often seen in the context of heart failure (with and without preserved EF), atrial fibrillation/flutter, opiate treatment and as a secondary effect of PAP therapy of OSA. In this case, CSA was confirmed to present prior to the application of PAP therapy, worsened on PAP and occurs in the context of preserved EF. Therefore, the most likely explanation is either treatment emergent CSA or atrial fibrillation cardiac rhythm related CSA.
4. CPAP therapy is not universally effective for CSA.
5. In appropriately selected patients with CSA, ASV therapy can be effective at normalizing AHI and alleviating sleep apnea symptoms [41].

## Case 3

### History and clinical features

DA is female first seen when she was 24 years old and presented with spontaneous onset of irresistible EDS with onset at age 21 years. EDS manifested as unintended dozing while studying and when driving. She reported hypnagogic hallucinations but not sleep paralysis and cataplexy. Dream recall was regular, vivid and sometimes accompanied daytime sleep. EDS occurs despite self-reported sleep duration of 8 hours per night plus twice weekly 30-45 minute naps and sleeps efficiency of 95%. Her boyfriend described snoring and witnessing apnea. DA's past medical and surgical history

was unremarkable. Alcohol was consumed at a rate of 6 cocktails per week and she used 2 cans of caffeinated soda daily. There is no history of illicit drug use. She did smoke 1 cigarette per day, a habit she acquired at age 20 years. Her family history was remarkable for OSA in her father.

Salient features on physical examination include a neck circumference of 14 inches with body mass index (BMI) of 27 kg/m<sup>2</sup>. The appearance of the oral pharyngeal airway is Mallampati class II with +3 tonsils and normal uvula and tongue. The maxillary overjet is 1 mm. The STOP BANG questionnaire score was 3, a value predictive of OSA [14].

OSA was suspected and diagnostic PSG was ordered but was negative for OSA. An investigation for a primary central hypersomnia syndrome followed. Her sleep logs showed stability and sleep-wake pattern with average time in bed 8.5 hours per night. PSG consisted of 437 minutes of sleep of which 25% was REM. The REM sleep latency was 4 minutes, consistent with a sleep onset REM period (SOREM). Nearly the entire recording was conducted when she was in the supine position. AHI and RDI was 2 and 3, respectively. Oxyhemoglobin saturation nadir was 96%. Periodic limb movement index was 1. Multiple sleep latency test (MSLT) conducted on the day following PSG had mean sleep latency of 3.9 minutes and 4 SOREM in a 5 nap protocol, findings consistent with narcolepsy as the cause of her EDS [42]. Treatment with alertness promoting substances proved effective at controlling symptoms until 8 years later when DA presented with worsening hypersomnia despite using methylphenidate at doses that had typically been fully effective. Her BMI was now 33.7 kg/m<sup>2</sup> and snoring was said to be louder and more disruptive. Reassessment with diagnostic PSG was diagnostic of OSA with an AHI 8, RDI 29 and oxyhemoglobin saturation nadir of 90%. Subsequent PSG for titration of PAP confirmed control of OSA with PAP and domiciliary treatment with PAP restored subjective alertness without requiring an increase in the dose of methylphenidate.

### Discussion

DA presented with EDS, loud snoring and witnessed apnea, features that are consistent with increased risk of moderate to severe OSA [16] making HSAT or PSG appropriate for diagnosis. However, full night attended diagnostic PSG was not diagnostic of sleep apnea. An evaluation for a primary central hypersomnia syndrome is warranted in cases where EDS is clinically relevant and the diagnostic PSG fails to confirm sleep apnea [43,44].

Components of REM sleep occurring while awake and in sleep transitions such as hypnagogic and hypnopompic hallucinations, sleep paralysis, and cataplexy are collectively termed dissociated REM sleep phenomena. Of these, cataplexy is nearly pathognomonic of narcolepsy but all occur more often in EDS caused by narcolepsy than in other causes of EDS. DA did not have cataplexy but there were clinical features consistent with hypnagogic hallucinations and she manifested vivid dreaming and dreaming during naps, features suggesting increased REM pressure and favoring narcolepsy as a potential cause of EDS.

EDS can be quantified by the use of the MSLT [42] and the diagnosis of narcolepsy requires fulfillment of specific clinical, PSG and MSLT (Table 3) criteria or the demonstration of cerebral spinal fluid hypocretin-1 concentration, assayed by immunoreactivity, that is less than or equal to 110 pg/ml or less than one third of mean values obtained in normal subjects with the same standardized assay [1]. MSLT data derived by a standardized protocol was diagnostic of narcolepsy [45].

ICSD-3 [1] classifies narcolepsy into Type 1 (narcolepsy with cataplexy) and Type 2 (narcolepsy without cataplexy). Type 1 is prevalent in 0.02% - 0.18% in the US and Western European populations and in 0.16% - 0.18% in the Japanese populations. The prevalence of Type 2 disease is not known but estimated to be higher than that of Type 1 narcolepsy. Lacking features of cataplexy, DA was diagnosed with Type 2 narcolepsy and treated with alertness promoting substances [43] with clinically significant beneficial effect. Recurrence of EDS occurred in the context of a 25% increase in BMI and coincides with more disruptive snoring and bed partner observed apnea. Reassessment with PSG demonstrated moderate OSA coincident with pre-existing Type 2 narcolepsy. The addition of PAP therapy restored alertness to normal levels thereby establishing a causal relationship between the developments of OSA in the recurrence of EDS.

### Key learning points

1. There are numerous causes of EDS such that establishing a diagnosis can be complex. In the case of DA, the clinical history on presentation and results of standardized questionnaires were predictive of OSA. However, irresistible EDS, age of symptom onset, the occurrence of hypnagogic hallucinations, regular dream recall and dream recall after naps are atypical features in OSA but not so in narcolepsy [46].

2. In cases where OSA is likely, an evaluation for a primary central hypersomnia syndrome cannot proceed without first excluding OSA or, if OSA is confirmed, controlling OSA with PAP. The diagnostic hallmark of narcolepsy is the presence of physiologic sleepiness (mean sleep latency on MS LT  $\leq$  8 minutes) and  $\geq$  2 SOREM on MSLT and prior night PSG. Individuals with untreated OSA can have MSLT findings consistent with narcolepsy [47]. However, in contrast to those with narcolepsy, short sleep latency and frequent SOREMs in sleep apnea resolves with adequately adjusted and consistently used PAP therapy.

3. OSA can coexistent and/or complicate existing sleep disorders as it occurred in this case [2,11].

4. The recurrence of EDS occurred while the patient was on previously effective doses of alertness promotion therapy and coincided with significant weight gain and worsening of snoring. There is a strong relationship between OSA and obesity with increasing prevalence and severity of OSA with increases in BMI [26].

5. Patient reported questionnaires like the STOP BANG [14] and others [48], while of value in assessing pretest probability and severity of OSA, are not sufficient to establish the diagnosis of sleep apnea [16].

### Summary

The previous several decades ushered significant expansion in the study of sleep and its disorders leading to the acceptance of sleep medicine as a formal discipline of medicine. ICSD-3 [1] provides

the framework to describe and categorize currently accepted sleep disorders and it further serves to illustrate the diversity of sleep disturbances. In this manuscript, we offer a case based introduction into the diagnosis and management of selected disorders of sleep with emphasis on SDB syndromes.

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