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Obstructive sleep apnea syndromes

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The first description of an obstructive sleep apnea (OSA) sufferer is generally attributed to the novelist Charles Dickens, who described ''Joe'' in *The Posthumous Papers of the Pickwick Club*, published in 1836. Joe was an excessively sleepy, obese boy who snored loudly and had possible right-sided heart failure that led to his being called ''young dropsy'' [1,2]. The first physician to describe the clinical features of OSA was Broadbent in 1877 [3]. Wells reported in 1898 curing several patients of sleepiness by treating their upper airway obstruction [3]. Burwell et al studied obese patients with somnolence, attributed their somnolence to hypercapnia, and coined the term ''pickwickian'' in 1956 [2,4]. In 1965, Gastaut et al [5] in France and Jung and Kuhlo [6] in Germany described sleep apnea and its associated polysomnographic findings. In 1972, in Rimini, Italy, Lugaresi and Sadoul organized the first international symposium on ''Hypersomnia with Periodic Breathing,'' mostly devoted to the dismemberment of the pickwickian syndrome, and reports, particularly by Coccagna et al, on hemodynamic changes associated with abnormal breathing during sleep. Guilleminault et al [7] reported the presence of sleep apnea in narcolepsy and insomnia at the 1972 Rimini meeting and characterized insomnia with sleep apnea as a new syndrome in 1973 [8]. Guilleminault et al coined the terms ''sleep apnea syndrome'' and ''obstructive sleep apnea syndrome'' in 1976 to emphasize the occurrence of this syndrome in nonobese patients. In the same year, they reported the existence of this syndrome in children. Completing the loop of hypersomnolence and insomnia and extending the spectrum of sleep apnea syndromes, in 1982 Guilleminault et al reported the

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ResMed
Exhibit 1013 - Page 1

presence of abnormal respiratory efforts during sleep without apneas in children and gave the name "upper airway resistance syndrome" (UARS) in 1993 after a similar description in adults [9].

Treatment of sleep apnea advanced significantly when Kuhlo et al [10] in 1969 and Lugaresi et al [11] in 1970 reported that tracheotomy was an efficacious treatment for sleep apnea. Guilleminault et al [12] confirmed in 1981 long-term efficacy of tracheotomy in 50 OSA patients who had complete relief of clinical symptoms, return to full activity, and normal adaptation to social and familial life. Although Ikematsu popularized uvulopalatopharyngoplasty (UPPP) for the treatment of snoring in 1964, it was not until 1981 that Fujita performed the first UPPP as a treatment for OSA [3]. Sullivan et al [13] devised the first nasal continuous positive airway pressure (CPAP) machine and in 1981 reported its efficacy in the treatment of sleep apnea [3]. Riley et al [14] developed new maxillomandibular procedures in the 1980s for subjects intolerant to nasal CPAP.

Epidemiology

OSA can affect various age groups. The prevalence of adult OSA in the United States has been reported to be 4% in men and 2% in women between the ages of 30 and 60 years [15]. The actual prevalence, however, may be higher. Young et al [16] estimated that among middle-aged adults, 93% of women and 82% of men with OSA have not been clinically diagnosed [16]. The Wisconsin Sleep Cohort study evaluated the association of premenopause, perimenopause, and postmenopause with sleep-disordered breathing (SDB) in a group of 589 women [17]. Using multivariate regression analysis adjusted for age, body habitus, smoking, and other potential confounding factors, Young et al [17] calculated the odds ratios (95% CI) for apnea-hypopnea index (AHI) greater than five events per hour of sleep to be 1.2 (range 0.7–2.2) with perimenopause and 2.6 (range 1.4–4.8) with postmenopause. These results suggest that the menopausal transition is significantly associated with an increased risk of SDB independent of known confounding factors [17]. After menopause, women develop OSA at a rate similar to men [18,19]. The maximum prevalence of OSA occurs between the fifth and seventh decades [18]. Obesity increases the risk of developing OSA, and race may be a risk factor. The incidence of OSA is reportedly increased in Pacific Islanders, Mexican-Americans, and blacks [20–22]. The higher prevalence of OSA among blacks reported by Redline et al [22] was more pronounced in individuals less than 25 years of age and was not accounted for by differences in body mass index (BMI) or by differences in exposure to alcohol and tobacco. Variable age of puberty, speed of development of secondary characteristics, and mucosal enlargement associated with hormonal surge may have biased these findings [23]. In contrast, a study in New Zealand comparing sleep apnea severity among Maori, Pacific Islanders, with Europeans reported that race was not an

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Exhibit 1013 - Page 2

important predictor of severity when adjusted for factors, such as neck size, BMI, and age [24].

Clinical presentation

Adult sleep-disordered breathing

SDB encompasses the spectrum from severe to mild OSA to UARS. The categorization into two different syndromes is still controversial; the important issues include recognizing the different signs and symptoms, adequately exploring respiration during sleep, understanding and choosing the necessary polygraphic montages, and using the appropriate criteria to arrive at a valid diagnosis. Diagnostic criteria for SDB include either excessive sleepiness or insomnia with frequent episodes of obstructed breathing during sleep and associated features of loud snoring, morning headaches, and dry mouth on awakening [25].

Daytime sleepiness is the most common complaint among patients with OSA. It can occur following meals, while sitting as a passenger in a car, watching television, attending a meeting or a lecture, eating, talking, or even while driving. Patients may notice difficulty with attention, concentration, memory, judgment, and impaired performance of tasks requiring dexterity. Approximately 50% of patients report generalized, dull, morning or nocturnal headaches [26]. About a third of patients at the Stanford Sleep Disorders Clinic have reported sexual dysfunction, either decreased libido or impotence. In a prospective study of 25 OSA patients with AHI greater than 10, Farfulla et al [27] reported abnormal bulbocavernosus reflex (either prolonged latency or reduced amplitude) in 68% of these patients. These abnormalities correlated significantly with the severity of OSA and the severity of gas exchange alterations, but did not vary with age [27].

Nocturnal symptoms in OSA are more specific than daytime symptoms. Loud snoring with brief gasps alternating with episodes of silence lasting from 20 to 30 seconds occurs frequently [26,28]. Seventy-five percent of spouses report apneic episodes terminated by gasps, choking sounds, snorts, vocalizations, or brief awakenings [29]. Diaphoresis in the neck and upper chest area and restlessness manifested as tossing and turning, probably caused by increased respiratory effort related to upper airway obstruction, has been described in about half of the patients. Eighteen percent to 31% of patients with OSA syndrome report a sensation of choking or dyspnea interrupting sleep [26,28,30,31]. Dyspnea may be caused by increased pulmonary wedge pressure resulting from increased venous return from the extremities secondary to decreased intrathoracic pressure during episodes of upper airway obstruction. Other nocturnal symptoms include nocturia (28%); esophageal reflux; dryness of the mouth (74%); and drooling (36%) [26,28].

Physical examination findings in OSA include obesity (BMI >28 kg/m^2); neck circumference greater than 40 cm (Kushida et al [32] reported

ResMed
Exhibit 1013 - Page 3

sensitivity of 61% and specificity of 93% for OSA regardless of gender); nasal turbinate hypertrophy; septal deviation; high and narrow hard palate; elongated low-lying uvula; redundant and low-lying soft palate; crowding of the oropharynx with enlarged tonsils and adenoids; prominent tonsillar pillars; macroglossia; narrow maxilla; narrow mandible; overjet and retrognathia; cross-bite; and dental malocclusion.

Adult upper airway resistance syndrome

In a series of 400 UARS patients, Guilleminault et al [33,34] reported that 56% were women, 32% were of East Asian origin, and the mean age was 38 ± 14 years. This sex, race, and age distribution varies from that typically seen in OSA. Unlike OSA patients, who usually complain of daytime sleepiness, UARS patients frequently complain of insomnia, sleep fragmentation, and fatigue, and their psychologic profile reveals high anxiety. Other clinical features of UARS patients include cold extremities; postural hypotension; history of fainting; low mean systemic arterial blood pressure; orthostasis on tilt table testing; myalgias (sometimes corresponding to the characteristic pain points associated with fibromyalgia); and functional somatic complaints [35]. During sleep, the arousal threshold in UARS patients is lower than OSA patients, thereby allowing the patient to awaken in response to small increases in inspiratory effort, compared with OSA patients, whose arousal thresholds require higher inspiratory pressures up to −40 to −80 cm H_2O and decrease in oxygen saturation. During sleep, UARS patients demonstrate an increase in alpha rhythm and a relative increase in delta sleep, whereas OSA patients show a predominance of stage 1 and 2 non–rapid eye movement (REM) sleep with a decrease in delta sleep. The difference between UARS and OSA patients is hypothesized to be caused by genetically predetermined and environmentally altered pharyngeal receptors, particularly mechanoreceptors: patients with UARS may have intact, sensitive, peripheral pharyngeal function, whereas OSA patients may have primary pharyngeal receptor dysfunction [35].

Sleep-disordered breathing syndromes and insomnia

OSA and more often UARS patients may present with complaints of insomnia (problems with sleep maintenance or unrefreshing sleep) similar to patients with primary insomnia, such as psychophysiologic insomnia. Other SDB-associated manifestations, however, such as snoring, choking-gasping-snorting, frank apneic episodes, nocturia, reflux, and hypertension, together with objective findings suggestive of upper airway obstruction may provide clues to the presence of disordered breathing during sleep as the underlying etiology. History of trying too hard to sleep, conditioned arousal to bedroom or sleep-related activities, evidence of increased somatized tension (agitation, muscle tension, or increased vasoconstriction), or prolonged wake after sleep onset associated with racing thoughts and heightened

ResMed
Exhibit 1013 - Page 4

arousal, together with normal physical examination, may suggest psychophysiologic insomnia, despite the fact that conditioned sleep-onset insomnia may developed secondary to the nocturnal sleep disruption induced by the SDB.

Syndromes criteria and severity classification

SDB is characterized by transient upper airway resistance, repetitive reduction or cessation of airflow caused by partial or complete occlusion of the upper airway during sleep, associated with fragmentation of sleep, arousals, bradytachycardia, and more or less oxygen desaturation, despite the presence of increasing respiratory effort. Apnea in adults is defined as the cessation of airflow for greater than or equal to 10 seconds. Various criteria have been utilized to define hypopnea, including (1) greater than 50% reduction in the amplitude of breathing from baseline during sleep, or (2) less than 50% reduction in the amplitude of breathing during sleep associated with either greater than 3% oxygen desaturation or an arousal, or (3) greater than 30% reduction in the amplitude of breathing during sleep or 30% reduction in the nasal cannula-pressure transducer curve associated with oxygen desaturation greater than or equal to 4%, and (4) event duration greater than or equal to 10 seconds [35,36]. Respiratory event-related arousals consist of limitation of flow greater than or equal to 10 seconds and terminating in an arousal associated with snoring. Introduction of the nasal cannula–pressure transducer system and esophageal pressure (Pes) monitoring has led to recognition of various patterns of increased respiratory effort that disrupt sleep but are not apneas or hypopneas, such as Pes crescendo (a progressive increase in Pes) and sustained continuous effort (a persistent increase in Pes without any crescendo, over several epochs). These events terminate in Pes reversal (an abrupt drop in Pes) that occurs independently of the electroencephalogram pattern, which may be an alpha electroencephalogram arousal, a burst of delta activity, or no visually seen change in electroencephalogram pattern.

Although the authors believe that UARS clearly represents a syndrome distinct from OSA, in evaluating SDB the American Academy of Sleep Medicine Task Force in 1999 included UARS in the OSA-hypopnea syndrome and defined it as the demonstration of five or more obstructive apneas-hypopneas or respiratory event-related arousals per hour of sleep and none of the new patterns easily identified with appropriate recording techniques have been integrated well [35,36]. This deficiency means that minutes of increased respiratory effort with unstable sleep are currently not tabulated in many clinical polysomnograms, and real impairment of subjects is underestimated, particularly in UARS subjects. OSA can be classified based on the apneas plus hypopneas per hour of sleep index (AHI) or respiratory disturbance index ([RDI] apneas plus hypopneas plus

ResMed
Exhibit 1013 - Page 5

respiratory event-related arousals per hour of sleep) into mild (5< AHI or RDI <15); moderate (15< AHI or RDI <30); or severe (AHI or RDI >30). UARS has been defined as having a RDI less than 4 and arterial oxygen saturation (Sao_2) greater than 93%.

Polysomnography and other tests

Overnight pulse oximetry has occasionally been used as a screening test to identify patients with sleep apnea, but it is not a substitute for polysomnography because of its inability to detect UARS and apneas or hypopneas with arousal but unassociated with significant desaturation [37,38]. Full-night polysomnography is routinely indicated for patients suspected of having OSA syndrome [37–39]. Pes monitoring during polysomnography recording is the reference standard in detecting respiratory effort [36,37]. Pulse transit time measures the transmission time for the arterial pulse pressure wave to travel from the aortic valve to the periphery and increases during inspiratory falls in blood pressure and decreases during arousal-induced increases in blood pressure. Pulse transit time has a high sensitivity and specificity in distinguishing between central and obstructive apnea-hypopnea [37] and may be used if Pes monitoring is not available. Polysomnography monitoring in adult OSA demonstrates greater than five obstructive apneas per hour of sleep, lasting at least 10 seconds and associated with one or more of the following: (1) frequent arousals from sleep; (2) bradytachycardia; and (3) arterial oxygen desaturation [25]. Fig. 1 depicts the polysomnographic findings in a patient with OSA.

In some circumstances, split-night full-night polysomnography may be considered [37–40]. During split-night full-night polysomnography recordings, the first half of the night is spent in diagnostic recording, with the second half of the night used for CPAP titration. In a consensus statement, Loube et al [40] formulated these guidelines: split-night studies may be considered in patients with RDI greater than 40 events per hour during the first 2 hours of a diagnostic polysomnography, of which the final portion is used to titrate CPAP; patients with RDI between 20 and 40 events per hour may undergo a split-night study based on the occurrence of obstructive respiratory events of prolonged duration or associated with severe oxygen desaturation; a minimum of 3 hours of sleep is recommended for adequate titration; the split-night study requires the recording and analysis of the same parameters as a standard diagnostic full-night polysomnography; and an additional full-night CPAP titration may be required if the split-night study does not allow for abolishment of most obstructive events or if the prescribed CPAP treatment does not control clinical symptoms. Split-night studies can potentially underestimate the severity of OSA, however, because breathing abnormalities are usually worse during REM sleep in overweight

ResMed
Exhibit 1013 - Page 6

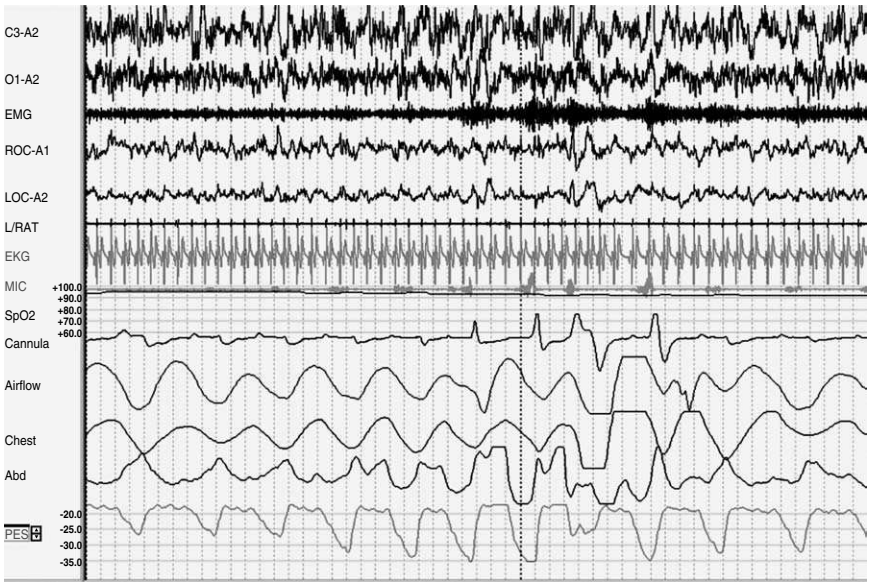

Fig. 1. Polysomnogram of a patient with OSA. The cannula and airflow channels demonstrate reduction in oronasal airflow consistent with a hypopnea. Paradoxical respiration is noted on the chest and abdominal effort channels. Esophageal pressure crescendo with Pes reversal associated with an arousal is seen.

patients, and the longest REM sleep periods are in the second half of the night. In addition, CPAP titration during split-night recordings may be suboptimal because of the shorter time spent on titration.

Limited-channel diagnostic full-night polysomnography (cardiorespiratory sleep studies) may be adequate [40–42] in patients who have a high pretest probability of OSA based on validated screening algorithms [30,32]. Minimum parameters recorded and measured in limited-channel full-night polysomnography are oronasal airflow, chest wall respiratory effort, electrocardiogram, and oxyhemoglobin saturation [42]. These limited sleep studies, however, cannot effectively distinguish sleep from wake or determine sleep stage, are less accurate than standard full-night polysomnography in determining the number of obstructive respiratory events, and are unable to detect co-existing non-OSA sleep disorders. They cannot recognize UARS. They recognize subjects with severe problems [40,43]. Multiple sleep latency testing, which consists of four to five daytime naps during which sleep latency is measured, provides an objective measure of sleepiness and propensity to sleep. OSA patients may or may not demonstrate a mean sleep latency of less than 10 minutes (normal >10 minutes) [25]. Maintenance of Wakefulness Test is preferred by some to evaluate the propensity of subjects to stay alert.

ResMed
Exhibit 1013 - Page 7

Comorbid conditions

Hypertension

OSA is an independent risk factor for hypertension, and hypertension is a frequent comorbid condition with sleep apnea [44–47]. About 30% of patients with systemic hypertension have sleep apnea, whereas 50% or more of patients with sleep apnea have systemic hypertension [26,48]. Moller et al [49] performed 24-hour blood pressure monitoring and measured plasma levels of vasoactive hormones (renin, angiotensin II, aldosterone, atrial natriuretic peptide, brain natriuretic peptide, vasopressin, and endothelin-1) in 24 OSA patients and 18 control subjects. Compared with controls, OSA patients had significantly higher blood pressure and heart rate, and the sleep-related nocturnal blood pressure drop was reduced. Moreover, angiotensin II and aldosterone levels were significantly higher in OSA subjects compared with controls, with angiotensin II correlating positively with daytime blood pressure recordings. Thirteen OSA patients re-examined after 14 months of CPAP therapy demonstrated reduction in blood pressure, which correlated with a decrease in both plasma renin and plasma angiotensin II concentrations.

Brachial artery diameter and brachial artery flow-mediated dilation, which are surrogates of endothelial dysfunction, were measured in elderly participants in the Wisconsin Sleep Heart Health/Cardiovascular Health Study cohort (N = 1037; age >68 years; 56% women) [50]. After adjustment for BMI and other confounders, a statistically significant linear association between the hypoxemia index and baseline diameter was noted. This association was stronger among participants less than 80 years and among hypertensives. Nieto et al [50] suggested that vascular dysfunction may partially explain the relationship between OSA, hypertension, and cardiovascular disease. In another study, Sin et al [51] reported that 40% of 301 patients with congestive heart failure had OSA and systemic hypertension. After controlling for other risk factors, including obesity, OSA patients were 2.89 times (95% CI, range 1.25–6.73) more likely to have systolic hypertension (blood pressure $\geq$ 140 mm Hg) than those without OSA, and the degree of systolic blood pressure elevation was directly related to the frequency of obstructive apneas and hypopneas [51].

Hypertension associated with OSA may be generated by sympathetic overactivity triggered by intermittent hypoxemia, large negative fluctuations in intrathoracic pressure, and arousal from sleep [52,53]. Several studies have demonstrated reversal of sustained daytime hypertension by effective treatment of apnea through surgery [54,55] or nasal CPAP [56,57].

Cardiovascular disease

The Sleep Heart Health Study reported that OSA is associated with relative odds of 2.38 for heart failure, independent of other known risk

factors [58,59]. OSA has also been implicated in the pathogenesis of pulmonary hypertension, nocturnal cardiac ischemia, nocturnal arrhythmias, and atherosclerosis [46,48,60–64]. OSA patients demonstrate transient fluctuations in pulmonary artery pressure and pulmonary wedge pressure coincident with apneas, which may lead to progressive increase in pulmonary artery pressure. Permanent precapillary pulmonary hypertension at rest has been observed in some OSA patients and is reported to be poorly reversible after OSA treatment [63]. Various studies have demonstrated that OSA can precipitate nocturnal angina in patients with coronary artery disease [65–69]. Myocardial ischemia associated with OSA is postulated to result from a combination of increased left ventricular afterload, sympathoadrenal stimulation, and postapneic tachycardia [48]. In a study of 400 OSA patients conducted by Guilleminault et al [70], cardiac arrhythmias consisting of nonsustained ventricular tachycardia ($N = 8$), sinus arrest lasting 2.5 to 3 seconds ($N = 43$), second-degree atrioventricular conduction block ($N = 31$), and premature ventricular contractions ($N = 75$) were noted in 193 (48%) of subjects. A relationship between low Sao_2 (<75%) and presence of severe arrhythmias was shown. A prospective study of 147 consecutive patients demonstrated significantly higher prevalence of nocturnal paroxysmal asystole in OSA patients and increased episodes of bradycardia and pauses that correlated with the severity of the sleep apnea [61]. OSA has been linked to other risk markers for cardiovascular disease, including leptin, C-reactive protein, homocysteine, and insulin-resistance syndrome [71]. The independent role of OSA in these overweight and obese subjects is unclear.

Cerebrovascular disease

The relationship between OSAS and cerebrovascular disease is bidirectional. Habitual snoring increases the risk of cerebrovascular disease with odds ratios (95% CI) ranging from 2.1 to 3.3 [72–75]. Sixty-nine percent to 95% of patients with acute strokes or transient ischemic attacks has OSA [76,77]. One hundred fourteen male snorers, 40 to 65 years of age, with complaints of disturbed sleep underwent ultasonographic examination of both carotid arteries to evaluate intima-media thickness and the presence of plaque. The study revealed significantly higher intima-media thickness values in OSA patients compared with habitual snorers. Age and BMI were significantly associated with intima-media thickness, whereas age and RDI were most predictive for plaque [78]. Kaynak et al [78] suggested that SDB may be a predisposing factor for atherosclerosis and may precipitate plaque formation. Proposed mechanisms underlying increased risk of stroke in OSA patients are multifactorial and include hypertension, reduction in cerebral blood flow, altered cerebral autoregulation, impaired endothelial function, accelerated atherogenesis, thrombosis, and paradoxic embolism [79].

ResMed
Exhibit 1013 - Page 9

Obesity-metabolic syndrome

Approximately 60% to 90% of OSA patients are obese [80]. Obesity is the most common metabolic abnormality seen with sleep apnea and is predominantly central in pattern. BMI, body weight, and the sum of fat skin folds are good predictors for the degree of OSA [80,81]. The percentage of body fat and BMI are good predictors of AHI greater than 10, with high sensitivity (95.5%) but low specificity (46.2%) [81]. A review of MRI scans demonstrated a significant correlation between AHI and intra-abdominal and subcutaneous abdominal fat, but no correlation was established with subcutaneous fat in the neck region or parapharyngeal fat in the airway vicinity [81]. Leptin concentrations correlate with AHI and with biochemical markers of the metabolic syndrome (lipoproteins, glucose) [81]. Vgontzas et al [82] have demonstrated elevations of interleukin-6, tumor necrosis factor-alpha, leptin, and insulin levels in sleep apnea, independent of obesity [82]. Upper body obesity is linked to increased risk of diabetes, hyperlipidemia, insulin resistance and hyperinsulinemia, hyperuricemia, hypertension, and cardiovascular or cerebrovascular disease [83,84]. OSA has been implicated as an independent risk factor for insulin resistance, a known risk factor for atherogenesis [9], but this independence has been challenged by other data.

Treatment

Treatment for symptomatic OSA syndromes is influenced by the severity of sleep apnea, relative efficacy of treatment options, the presence of comorbid conditions, and patient and physician preference. For mild forms of OSAS, nonsurgical options include (1) weight loss; (2) avoidance of sleep deprivation, alcohol, nicotine, and sedatives; (3) positional therapy (avoidance of the supine posture); and (4) treatment of comorbid conditions, such as hypothyroidism. Pharmacologic treatment of sleep apnea has not been very successful [85,86]. The use of stimulants, however, such as modafinil, 200 to 400 mg/d, may be useful as adjunctive therapy for daytime sleepiness that persists despite optimization of CPAP therapy. Oral appliances are useful for mild OSA and for patients with moderate or severe OSA who are unable or unwilling to tolerate CPAP and who have failed surgery or are not surgical candidates. Oral appliances work by increasing airway space, providing a stable anterior position of the mandible, advancing the tongue or soft palate, and possibly by changing genioglossus muscle activity [87,88]. These devices are not well tolerated by patients with significant temporomandibular joint symptoms.

Positive airway pressure therapy (continuous, bilevel, and autotitrating)

CPAP therapy can be used for all categories of OSA and represents first-line therapy for moderate to severe OSA. Based on the risk of increased

ResMed
Exhibit 1013 - Page 10

hypertension documented in the Wisconsin sleep cohort data, Loube et al [40] recommend CPAP therapy for all OSA patients with RDI of 30 events per hour. Similarly, based on documented improvement in symptoms and daytime function in CPAP-treated patients, Loube et al [40] recommend CPAP therapy for patients with RDI of 5 to 30 events per hour associated with symptoms of excessive daytime sleepiness; impaired cognition; mood disorders; insomnia; documented cardiovascular diseases (including hypertension and ischemic heart disease); or stroke. For Loube et al [40], treatment with CPAP is not indicated for asymptomatic, mild OSA patients without evidence of cardiovascular disease.

Effective CPAP therapy reduces nocturnal respiratory disturbances and improves nocturnal oxygenation, sleep architecture, daytime sleepiness, neurocognitive performance, driving performance, and perceived health status [89,90]. Cardiovascular end points, such as hypertension, cardiac arrhythmia, nocturnal ischemia, left ventricular function, and mortality, may also improve with CPAP therapy [89]. Health care use is also reduced in OSA patients on CPAP therapy compared with untreated patients.

Seventy-six percent of OSA patients who were offered a trial of CPAP took their machines home [91]. In addition to patients declining CPAP, patient compliance and adherence remain major issues. Compliance refers to the proportion of patients using CPAP machines that are delivering a preset level of pressure, whereas adherence refers to the proportion of patients prescribed CPAP who report continued usage [92]. Compliance rates assessed through patient self-reported usage of CPAP nightly range from 63% to 90% [90,92]. In one study when compared with objective measures, patients overestimated the number of hours of use by 69 minutes $\pm$ 110 minutes, and 14% of subjects erroneously reported nightly usage of CPAP [93]. Kribbs et al [93] defined CPAP failure as usage of CPAP less than 4 hours per night on 70% of the nights or lack of symptomatic improvement. Objectively measured CPAP usage adjusted to reflect mask-on time demonstrated average nightly use to be only 4.97 hours (range 2.8–6.9) [90]. The hallmark for eventual nonadherence and rejection of CPAP is use of CPAP less than 4 hours per night [90]. Reasons for nonadherence cited by patients at the Stanford Sleep Disorders Clinic are similar to those reported by others [90,92]: (1) nuisance factors (noise, partner intolerance, inconvenience); (2) mask problems (leaking mask, mask rubbing, skin rash or abrasion, conjunctivitis); (3) side effects (nasal congestion, rhinorrhea, epistaxis, sinus discomfort, oronasal dryness, chest discomfort, aerophagia, claustrophobia, difficulty exhaling, pneumothorax [rare], pneumocephaly [rare]); and (4) incomplete resolution of symptoms (frequent awakening, persistent fatigue or sleepiness). CPAP pressure has not been found to be a determinant of long-term use [89].

Interventions to improve CPAP use are based on patient education and behavioral principles of positive reinforcement. These include providing literature addressing sleep apnea and good sleep habits; disseminating

ResMed
Exhibit 1013 - Page 11

information on CPAP use, benefits, and potential side-effects; organizing group educational sessions and support groups (eg, AWAKE groups); teaching adaptation skills to the patient and bed partner; scheduling regular clinic follow-up to monitor CPAP meter readings, discuss patient-perceived problems, and initiate treatment plans addressing identified problems; and implementing regular follow-up telephone calls (initially weekly, then monthly). Interventions mostly involve spending time with patients to determine the best nasal interface with least amount of sleep disruption, having common sense, and taking into consideration age and health status of the patient.

Bilevel positive airway pressure allows independent adjustment of inspiratory and expiratory pressures. Indications for a trial of bilevel positive airway pressure may include OSA patients who cannot tolerate CPAP because of persistent massive nasal mask air leak or discomfort exhaling against positive pressure, or have concomitant nocturnal breathing disorders, such as restrictive thoracic disorders, chronic obstructive pulmonary disease, or nocturnal hypoventilation [40].

Autotitrating positive airway pressure devices detect snoring, apneas, hypopneas, flow limitation, and changes in airway resistance or impedance, which are then interpreted by a central processing unit based on specific diagnostic algorithms to determine the resultant voltage for the autotitrating positive airway pressure blower in response to these signals [89,94]. The 2002 American Academy of Sleep Medicine practice parameters on autotitrating positive airway pressure indicate that (1) the diagnosis of OSA must be established by an acceptable method; (2) autotitrating positive airway pressure may be used during attended titration to identify a single effective pressure for use with standard CPAP; (3) autotitrating positive airway pressure may be used in self-adjusting mode for unattended treatment of OSA after an initial successful attended CPAP or autotitrating positive airway pressure titration; (4) patients being treated with fixed CPAP on the basis of an autotitrating positive airway pressure titration or being treated with autotitrating positive airway pressure require follow-up to determine treatment efficacy and safety; and (5) if symptoms do not resolve or if autotitrating positive airway pressure therapy is inefficacious, re-evaluation should be performed, and if needed, a standard CPAP titration should be done [94]. Autotitrating positive airway pressure devices are not recommended for split-night studies or for patients with congestive heart failure; significant lung disease (chronic obstructive pulmonary disease); daytime hypoxemia; respiratory failure; or prominent nocturnal oxygen desaturation other than from OSA [94]. Autotitrating positive airway pressure devices that rely on vibration or sound in the device's algorithm should not be used in patients who snore [94].

Surgical therapy of OSA is directed toward site-specific obstruction in the upper airway. The three major anatomic regions of obstruction for OSA are (1) the nose; (2) the palate (oropharynx); and (3) the base of the tongue

ResMed
Exhibit 1013 - Page 12

(hypopharynx). Fujita classified the sites of obstruction as follows: Fujita type I (palate with normal base of the tongue; Fujita type II (palate and base of the tongue obstruction); and Fujita type III (base of the tongue obstruction with normal palate).

Surgical techniques involve either extirpation of soft tissue, secondary soft tissue repositioning through primary skeletal mobilization, or bypass of the pharyngeal airway [95–97]. Procedures resulting in extirpation of soft tissue include UPPP; modified UPPP-extended uvulopalatal flap (discussed under the Stanford protocol later in this article); uvulopalatopharyngoglossoplasty; laser midline glossectomy; and lingualplasty [95]. UPPP, the most commonly used technique, enlarges the retropalatal airway through tonsillectomy (if present); trimming and reorientation of the posterior and anterior tonsillar pillars; and excision of the uvula and the posterior portion of the palate [95]. UPPP has a surgical response rate (defined as 50% reduction in AHI or RDI and a RDI below 20) ranging from 40% to 65% [95,97]. Analyzing 37 papers with a total of 640 patients, Sher and Goldberg [95] reported the following complications of UPPP: velopharyngeal insufficiency greater than 1 month (14 of 640); postoperative bleeding (7 of 640); nasopharyngeal stenosis (5 of 640); voice change (4 of 640); vague foreign body sensation (1 of 640); successfully managed airway obstruction (2 of 640); and death secondary to upper airway obstruction (1 of 640). UPPP has reported success rates ranging from 43% to 67% [95,98]. Powell et al [99] have described a modification of UPPP called uvulo-flap, which is less traumatic with less complication and at least similar success rate (see later).

Surgical techniques involving primary skeletal mobilization include transpalatal advancement pharyngoplasty, mandibular advancement, maxillomandibular advancement, genioglossal advancement, and hyoid myotomy and suspension [95]. Transpalatal advancement pharyngoplasty involves resection of the posterior hard palate with anterior advancement of the soft palate into the bony defect, thereby enlarging the retropalatal airway; it is used for persistent retropalatal obstruction after UPPP, but its role in the surgical armamentarium is still vague [95]. Mandibular advancement uses sagittal mandibular osteotomies to mobilize the tongue anteriorly and advance its insertion at the genioid tubercle; this procedure is beneficial for a small group of patients with class II dental occlusion and significant mandibular deficiency [95,96]. Maxillomandibular advancement involves Le Fort I maxillary and sagittal-split mandibular osteotomies with simultaneous advancement of both maxilla and mandible, thereby producing maximal enlargement of the retrolingual airway and some enlargement of the retropalatal airway [95,96].

Tracheotomy may be used to bypass the pharyngeal airway in OSA patients with morbid obesity; severe facial skeletal deformity (mandibular deficiency) with excessive daytime somnolence; hypoxemia (Sao_2 <70%); or significant cardiac arrhythmias [95,97]. The tracheotomy tube is plugged when the patient is awake to allow speech and swallowing. Although

ResMed
Exhibit 1013 - Page 13

tracheotomy is easy to perform and is effective for OSA, inconvenience and hygiene issues preclude its more widespread use.

The Stanford Protocol (Riley-Powell) surgical approach consists of a two-phased approach to direct surgical treatment of suspected regions of obstruction [95–97]. In conjunction with the clinical evaluation, patients undergo lateral cephalometry and fiberoptic endoscopy with Müller's maneuver. Phase I surgical intervention includes nasal reconstruction, UPPP or uvulopalatal flap, and limited mandibular osteotomy with genioglossus advancement. Nasal reconstruction is performed for patients with significant obstruction of the nasal airway (deviated septum, collapsed ala, or enlarged turbinates) [96]. In a series of 33 patients who underwent the modified UPPP-extended uvulopalatal flap surgery, the reported success rate was 81.8% [100], compared with the overall reported success rate of 60% for phase I surgery. Phase II surgery involves maxillomandibular advancement osteotomy to treat refractory hypopharyngeal (base of the tongue) obstruction by advancing the mandible at least 10 mm. The reported success rate for phase II surgery in 350 patients was 90% [96,97]. In a subgroup of 175 patients who underwent maxillomandibular advancement between 1998 and 1995, the mean age was 43.5 years, the cure rate was 97%, the mean hospital stay was 2.4 days, and the mean postoperative RDI was 7.2 compared with mean preoperative RDI of 72.3 [97].

Radiofrequency volumetric tissue reduction has been used for the treatment of turbinate hypertrophy and to reduce the base of the tongue [97,101]. In 18 patients treated with radiofrequency tongue-base reduction under local anesthesia with a mean of 5.5 sessions, mean RDI improved from 39.5 ± 32.7 to 17.8 ± 15.6 at 2.6 ± 0.7 months postoperatively [97]. Long-term follow-up (mean 28 ± 4 months) showed increase of RDI to 28.7 ± 29.4, with persistent improvement of the mean apnea index but with worsening hypopnea index and with mean weight increase of 3.1 ± 7.9 kg [97]. Performance of extra sessions improved results.

In the recent past orthognathic surgery has been performed. Maxillary expansion is routinely performed orthodontically, when there is constriction of the maxilla where posterior crossbite often exists. Although the width of the maxilla can be improved by expansion [102], it usually remains narrowed after expansion because the extent of expansion is limited by the width of the mandible, and mandibular constriction often coexists. Distraction osteogenesis, a process of bone lengthening by gradually separation of bone segments performed by simple osteotomy, has improved the ability to expand the mandible simultaneously with the maxilla. It has been performed by Li and Guilleminault [103] in six patients, improvement of SDB based on polysomnography and clinical results were seen in all six patients following maxillo-mandibular expansion, and no complications were encountered. The ideal candidate for this treatment may be an adolescent and young adult with isolated SDB who may be contemplating or are already in orthodontic treatment where lifelong CPAP treatment seems a limited alternative.

ResMed
Exhibit 1013 - Page 14

Surgery remains a viable alternative to nasal CPAP in OSA patients. The indications, risks, and complications of surgery, the possibility of multiple and staged procedures, and alternative forms of therapy need to be discussed with the patient. The selection of surgical procedures should be driven by the site of obstruction and the patient's airway anatomy, medical status, severity of sleep apnea, overall clinical status, age, patient preference, relative efficacy of the surgery, and the surgeon's experience and skill.

Summary

OSA syndromes afflict various age groups. OSA is reported to be more prevalent in middle-aged men (4%) compared with women (2%) in the United States, but the true prevalence may be higher, because OSA syndromes are underdiagnosed. This article reviews the history of sleep apnea, discusses the clinical presentation of OSA-hypopnea and UARS, and presents the pertinent physical examination findings and the results of sleep laboratory testing. Associated significant comorbid conditions (hypertension, cardiovascular and cerebrovascular disease, obesity-metabolic syndrome) are reviewed. Treatment options, both nonsurgical and surgical, are reviewed.

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ResMed
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