

## Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults

Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine

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**Background:** Obstructive sleep apnea (OSA) is a common chronic disorder that often requires lifelong care. Available practice parameters provide evidence-based recommendations for addressing aspects of care.

**Objective:** This guideline is designed to assist primary care providers as well as sleep medicine specialists, surgeons, and dentists who care for patients with OSA by providing a comprehensive strategy for the evaluation, management and long-term care of adult patients with OSA.

**Methods:** The Adult OSA Task Force of the American Academy of Sleep Medicine (AASM) was assembled to produce a clinical guideline from a review of existing practice parameters and available literature. All existing evidence-based AASM practice parameters relevant to the evaluation and management of OSA in adults were incorporated into this guideline. For areas not covered by the practice parameters, the task force performed a literature review and made consensus recommendations using a modified nominal group technique.

**Recommendations:** Questions regarding OSA should be incorporated into routine health evaluations. Suspicion of OSA should trigger a comprehensive sleep evaluation. The diagnostic strategy includes a sleep-oriented history and physical examination, objective testing,

and education of the patient. The presence or absence and severity of OSA must be determined before initiating treatment in order to identify those patients at risk of developing the complications of sleep apnea, guide selection of appropriate treatment, and to provide a baseline to establish the effectiveness of subsequent treatment. Once the diagnosis is established, the patient should be included in deciding an appropriate treatment strategy that may include positive airway pressure devices, oral appliances, behavioral treatments, surgery, and/or adjunctive treatments. OSA should be approached as a chronic disease requiring long-term, multidisciplinary management. For each treatment option, appropriate outcome measures and long-term follow-up are described.

**Keywords:** Obstructive sleep apnea; sleep evaluation; positive airway pressure treatment; oral appliance treatment; behavioral treatment; surgical treatment.

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Obstructive sleep apnea (OSA) is a common disorder affecting at least 2% to 4% of the adult population and is increasingly recognized by the public. The signs, symptoms and consequences of OSA are a direct result of the derangements that occur due to repetitive collapse of the upper airway: sleep fragmentation, hypoxemia, hypercapnia, marked swings in intrathoracic pressure, and increased sympathetic activity. Clinically, OSA is defined by the occurrence of daytime sleepiness, loud snoring, witnessed breathing interruptions, or awakenings due to gasping or choking in the presence of at least 5 obstructive respiratory

events (apneas, hypopneas or respiratory effort related arousals) per hour of sleep. The presence of 15 or more obstructive respiratory events per hour of sleep in the absence of sleep related symptoms is also sufficient for the diagnosis of OSA due to the greater association of this severity of obstruction with important consequences such as increased cardiovascular disease risk.<sup>1</sup>

The Practice Parameters of the American Academy of Sleep Medicine (AASM) present evidence-based recommendations for several aspects of the diagnosis and management of OSA. However, they do not present a comprehensive approach to OSA patients. The Board of Directors of the AASM assembled the Adult Obstructive Sleep Apnea Task Force in January 2007 to review available literature and produce a clinical guideline for the evaluation, management and long-term care of adult patients with OSA. This guideline is meant to assist primary care

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**Table 1**—AASM Levels of Recommendation

Term	Definition
Standard	This is a generally accepted patient-care strategy that reflects a high degree of clinical certainty. The term standard generally implies the use of Level 1 Evidence, which directly addresses the clinical issue, or overwhelming Level 2 Evidence.
Guideline	This is a patient-care strategy that reflects a moderate degree of clinical certainty. The term guideline implies the use of Level 2 Evidence or a consensus of Level 3 Evidence.
Option	This is a patient-care strategy that reflects uncertain clinical use. The term option implies insufficient, inconclusive, or conflicting evidence or conflicting expert opinion.

providers as well as sleep medicine specialists, surgeons, and dentists who care for patients with OSA.

### Guideline Development

All existing AASM practice parameters relevant to the evaluation and management of OSA in adults were incorporated into the development of this guideline. These parameters were previously developed via a computerized, systematic search of the scientific literature (for specific search terms and further details, see referenced practice parameters) and subsequent critical review, evaluation, and evidence grading. On the basis of these reviews the AASM Standards of Practice Committee developed practice parameters. Practice parameters were designated as “Standard,” “Guideline,” or “Option” based on the level and amount of scientific evidence available (Table 1).

The Adult OSA Task Force constructed the clinical guidelines from the current practice parameters. The practice parameters, which are updated every 5 years, were not revised by the task force. Consensus-based recommendations were developed to address important areas of clinical practice that had not been the subject of a previous AASM practice parameter, or where the available empirical data were limited or inconclusive. The Task Force held face-to-face meetings where members of the panel presented reviews of the current literature on consensus topics. Recommendations were generated by panel members and discussed by all. To minimize individual expert bias, the group voted anonymously and rated consensus recommendations using a modified nominal group technique.<sup>2</sup> All task force members voted on all questions. If a first round vote was inconclusive, a second anonymous vote was conducted. Consensus-based recommendations reflect the shared judgment of the committee members and reviewers, based on the literature and common clinical practice of topic experts. The consensus statements regarding the use of portable monitors were developed, employing similar methods, by the Portable Monitoring Task Force of the AASM for use in a previous guideline document.<sup>3</sup>

### Use of Practice Parameters and Clinical Guidelines

Practice parameters and clinical guidelines define principles of practice that should meet the needs of most patients in most situations. They should not, however, be considered exhaustive, inclusive of all available methods of care, or exclusive of other methods of care reasonably expected to obtain the same results. The ultimate judgment regarding appropriateness of any specific therapy must be made by the physician and patient in light

of the individual circumstances presented by the patient, available diagnostic tools, accessible treatment options, resources available, and other relevant factors. The AASM expects this clinical guideline to have an impact on professional behavior and patient outcomes. It reflects the state of knowledge at the time of publication and will be reviewed, updated, and revised as new information becomes available.

### Diagnosis

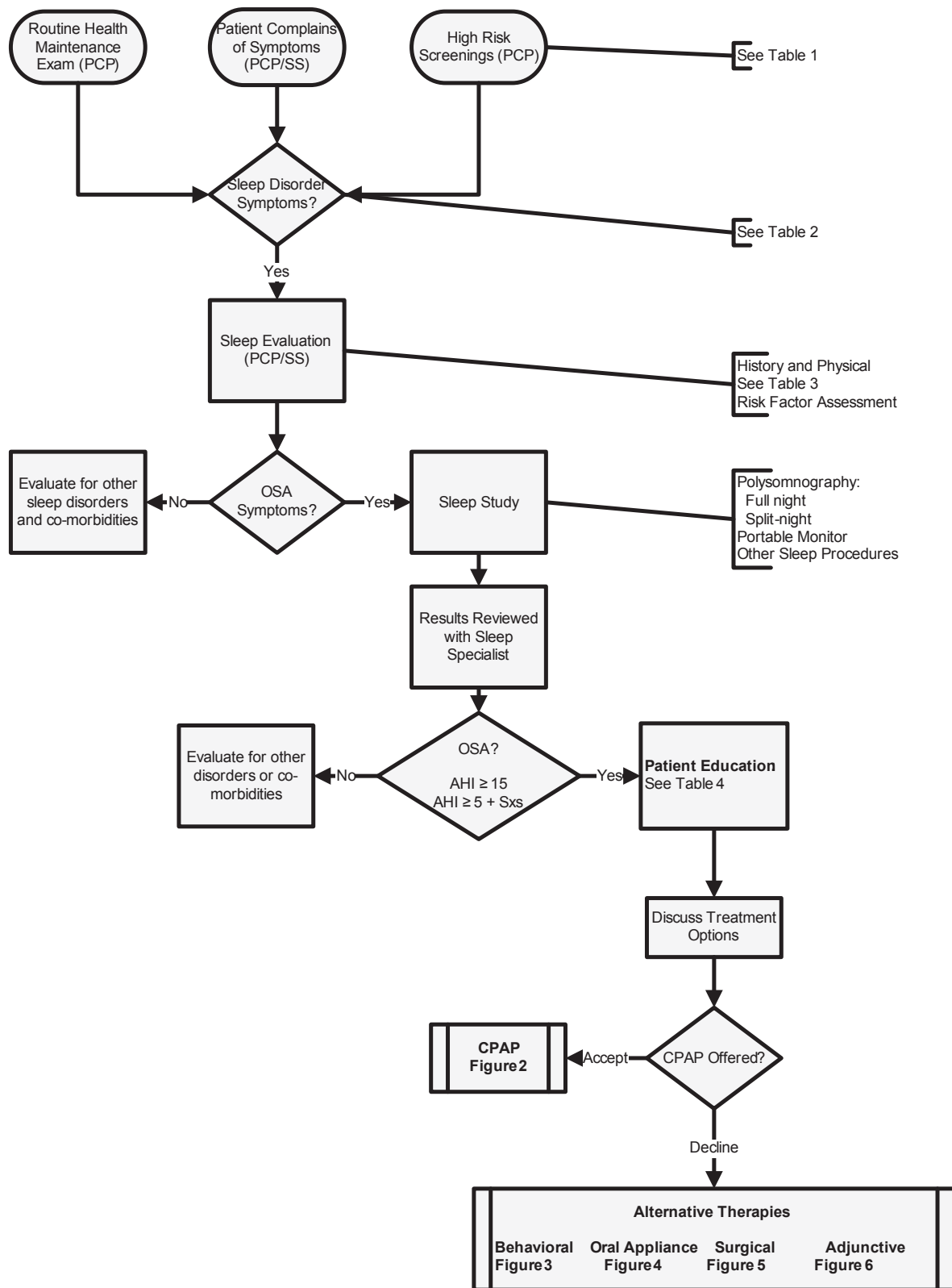
The presence or absence and severity of OSA must be determined before initiating treatment in order to identify those patients at risk of developing the complications of sleep apnea, guide selection of appropriate treatment and to provide a baseline to establish the effectiveness of subsequent treatment. Diagnostic criteria for OSA are based on clinical signs and symptoms determined during a comprehensive sleep evaluation, which includes a sleep oriented history and physical examination, and findings identified by sleep testing (Standard).<sup>4</sup> The overall evaluation of patients suspected of having OSA is summarized in Figure 1.

#### HISTORY AND PHYSICAL EXAMINATION

The diagnosis of OSA starts with a sleep history that is typically obtained in one of three settings: first, as part of routine health maintenance evaluation, second, as part of an evaluation of symptoms of obstructive sleep apnea, and third, as part of the comprehensive evaluation of patients at high risk for OSA. High-risk patients include those who are obese, those with congestive heart failure, atrial fibrillation, treatment refractory hypertension, type 2 diabetes, stroke, nocturnal dysrhythmias, pulmonary hypertension, high-risk driving populations (such as commercial truck drivers), and those being evaluated for bariatric surgery (Consensus). (Table 2)

Questions to be asked during a routine health maintenance evaluation should include a history of snoring and daytime sleepiness and an evaluation for the presence of obesity, retrognathia, or hypertension (Consensus). (Table 3) Positive findings on this OSA screen should lead to a more comprehensive sleep history and physical examination.

A comprehensive sleep history in a patient suspected of OSA should include an evaluation for snoring, witnessed apneas, gasping/choking episodes, excessive sleepiness not explained by other factors, including assessment of sleepiness severity by the Epworth Sleepiness Scale,<sup>5</sup> total sleep amount, nocturia, morning headaches, sleep fragmentation/sleep maintenance insomnia, and decreased concentration and memory (Consensus).



**Figure 1**—Evaluation. Flow chart for evaluation of patients suspected of having OSA. PCP = primary care physician, SS = sleep specialist.

(Table 4) An evaluation of secondary conditions that may occur as a result of OSA, including hypertension, stroke, myocardial infarction, cor pulmonale, decreased daytime alertness, and motor vehicle accidents, should also be obtained (Consensus).

The physical examination can suggest increased risk and should include the respiratory, cardiovascular, and neurologic

systems.<sup>6</sup> Particular attention should be paid to the presence of obesity, signs of upper airway narrowing, or the presence of other disorders that can contribute to the development of OSA or to the consequences of OSA. Features to be evaluated that may suggest the presence of OSA include increased neck circumference (> 17 inches in men, > 16 inches in women), body mass

**Table 2**—Patients at High Risk for OSA Who Should Be Evaluated for OSA Symptoms

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Obesity (BMI > 35)
Congestive heart failure
Atrial fibrillation
Treatment refractory hypertension
Type 2 diabetes
Nocturnal dysrhythmias
Stroke
Pulmonary hypertension
High-risk driving populations
Preoperative for bariatric surgery

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index (BMI)  $\geq 30$  kg/m<sup>2</sup>, a Modified Mallampati score of 3 or 4,<sup>7</sup> the presence of retrognathia, lateral peritonsillar narrowing, macroglossia, tonsillar hypertrophy, elongated/enlarged uvula, high arched/narrow hard palate, nasal abnormalities (polyps, deviation, valve abnormalities, turbinate hypertrophy) and/or overjet (Consensus).

Following the history and physical examination, patients can be stratified according to their OSA disease risk. Those patients deemed high risk should have the diagnosis confirmed and severity determined with objective testing in an expedited manner in order to initiate treatment. For other patients, the timing of further testing is determined by the risk of OSA and the presence of daytime impairment or associated morbidity. As part of the initial sleep evaluation, and prior to objective testing, patients should receive education regarding possible diagnoses, diagnostic steps, and the procedure involved in any testing (Consensus).

#### OBJECTIVE TESTING

The severity of OSA must be established in order to make an appropriate treatment decision.<sup>4</sup> No clinical model is recommended to predict severity of obstructive sleep apnea (Option),<sup>6</sup> therefore objective testing is required. A diagnosis of OSA must be established by an acceptable method (Standard).<sup>8</sup> The two accepted methods of objective testing are in-laboratory polysomnography (PSG) and home testing with portable monitors (PM). For specifics on the parameters to be measured with PSG and PM, see the sections below. PSG is routinely indicated for the diagnosis of sleep related breathing disorders (Standard).<sup>6</sup> PMs may be used to diagnose OSA when utilized as part of a comprehensive sleep evaluation in patients with a high pretest likelihood of moderate to severe OSA (Consensus).<sup>3</sup> PM testing is not indicated in patients with major comorbid conditions including, but not limited to, moderate to severe pulmonary disease, neuromuscular disease, or congestive heart failure, or those suspected of having a comorbid sleep disorder (Consensus).<sup>3</sup>

High-risk patients with nocturnal symptoms of OSA should undergo sleep testing, including those who are obese, those with systolic or diastolic heart failure (Standard), coronary artery disease (Guideline),<sup>6</sup> history of stroke or transient ischemic attacks (Option),<sup>6</sup> or significant tachyarrhythmias or bradyarrhythmias (Guideline).<sup>6</sup> Patients with congestive heart failure who continue to have nocturnal symptoms of sleep related breathing disorders despite optimal medical management are also at risk for OSA and should undergo testing (Standard).<sup>6</sup>

**Table 3**—Questions about OSA that Should Be Included in Routine Health Maintenance Evaluations

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Is the patient obese?
Is the patient retrognathic?
Does the patient complain of daytime sleepiness?
Does the patient snore?
Does the patient have hypertension?

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**Table 4**—OSA Symptoms that Should Be Evaluated during a Comprehensive Sleep Evaluation

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Witnessed apneas
Snoring
Gasping/choking at night
Excessive sleepiness not explained by other factors
Nonrefreshing sleep
Total sleep amount
Sleep fragmentation/maintenance insomnia
Nocturia
Morning headaches
Decreased concentration
Memory loss
Decreased libido
Irritability

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Patients with hypertension should undergo evaluation and testing if they have nocturnal symptoms (disturbed sleep, nocturnal dyspnea, or snoring) suggestive of obstructive sleep apnea or if they remain hypertensive despite optimal medical management (Consensus). A preoperative clinical evaluation that includes PSG or PM is routinely indicated to evaluate for the presence of OSA in patients before they undergo upper airway surgery for snoring or OSA (Standard).<sup>6</sup> A preoperative clinical sleep evaluation that includes PSG is recommended to evaluate for the presence of OSA in patients before they undergo bariatric surgery (Consensus). PM testing may also be indicated for the diagnosis of OSA in patients for whom in-laboratory PSG is not possible by virtue of immobility, safety or critical illness and to monitor response to non-CPAP therapies (Consensus).<sup>3</sup>

Follow-up PSG or attended cardiorespiratory (type 3 PM) sleep study is routinely indicated for the assessment of treatment results after surgical treatment for moderate to severe OSA (Standard).<sup>6</sup> To ensure satisfactory therapeutic benefit from oral appliances (OA), patients with OSA should undergo PSG or an attended cardiorespiratory (type 3 PM) sleep study with the OA in place after final adjustments of fit have been performed (Guideline).<sup>4</sup> Also, unattended PM may be indicated to monitor the response to non-CPAP treatments for OSA, including OAs, upper airway surgery, and weight loss (Consensus).<sup>3</sup> Follow-up PSG or attended cardiorespiratory (type 3 PM) sleep study is routinely indicated to assess treatment results after surgical or dental treatment for sleep related breathing disorders when symptoms return, despite a good initial response to treatment (Standard).<sup>6</sup> Follow-up PSG is routinely indicated in OSA patients for the assessment of treatment results on CPAP after substantial weight loss (e.g., 10% of body weight), substantial weight gain with return of symptoms, when clinical response is insufficient, or symptoms return despite a good initial response to CPAP (Standard).<sup>6</sup> Follow-up PSG or PM is not routinely

indicated in patients treated with CPAP whose symptoms continue to be resolved with CPAP treatment (Option).<sup>6</sup>

### Polysomnography

The use of PSG for evaluating OSA requires recording the following physiologic signals: electroencephalogram (EEG), electrooculogram (EOG), chin electromyogram, airflow, oxygen saturation, respiratory effort, and electrocardiogram (ECG) or heart rate.<sup>9</sup> Additional recommended parameters include body position and leg EMG derivations.<sup>9</sup> Anterior tibialis EMG is useful to assist in detecting movement arousals and may have the added benefit of assessing periodic limb movements, which coexist with sleep related breathing disorders (SRBD) in many patients (Standard).<sup>6</sup> An attended study requires the constant presence of a trained individual who can monitor for technical adequacy, patient compliance, and relevant patient behavior (Guideline).<sup>6</sup> Technical personnel should have appropriate sleep-related training. Current training pathways include on-the-job training utilizing the Accredited Sleep Technologist Education Program (A-STEP) or college-based training in a sleep technology program accredited by the Commission on Accreditation of Allied Health Education Programs (CAAHEP). The final pathway for demonstration of competency is certification, through the Board of Registered Polysomnographic Technologists (BRPT) or its equivalent. Technologist progression to certification is now required to meet AASM accreditation standards,<sup>10</sup> Center for Medicare and Medicaid Services Independent Diagnostic Testing Facility regulations,<sup>11</sup> and multiple state credentialing and licensing regulations.

The parameters, settings, filters, technical specifications, sleep stage scoring and event scoring should be done in accordance with the *AASM Manual for the Scoring of Sleep and Associated Events*.<sup>9</sup> The frequency of obstructive events is reported as an apnea + hypopnea index (AHI) or respiratory disturbance index (RDI). The definition of this index has varied over time. When an index is reported in this guideline it was taken directly from the specific practice parameter and the reader is referred to the source document for the definition. Every sleep study should be reviewed and interpreted by a qualified physician, as defined in the AASM Accreditation Standards (Consensus). Interscorer reliability assessment and other quality assurance measures should be performed on a regular basis. Formal written policies should be in place for all procedures. The most accepted measure of quality is sleep center or laboratory accreditation by the AASM (Consensus).

Full-night PSG is recommended for the diagnosis of a sleep related breathing disorder but a split-night study (initial diagnostic PSG followed by continuous positive airway pressure titration on the same night) is an alternative to one full night of diagnostic PSG.<sup>6</sup> The split-night study may be performed if an AHI  $\geq 40$ /hr is documented during 2 hours of a diagnostic study but may be considered for an AHI of 20-40/hr based on clinical judgment.<sup>6</sup> In patients where there is a strong suspicion of OSA, if other causes for symptoms have been excluded, a second diagnostic overnight PSG may be necessary to diagnose the disorder.<sup>6</sup>

The diagnosis of OSA is confirmed if the number of obstructive events (apneas, hypopneas + respiratory event related

arousals) on PSG is greater than 15 events/hr or greater than 5/hour in a patient who reports any of the following: unintentional sleep episodes during wakefulness; daytime sleepiness; unrefreshing sleep; fatigue; insomnia; waking up breath holding, gasping, or choking; or the bed partner describing loud snoring, breathing interruptions, or both during the patient's sleep.<sup>1</sup> OSA severity is defined as mild for RDI  $\geq 5$  and  $< 15$ , moderate for RDI  $\geq 15$  and  $\leq 30$ , and severe for RDI  $> 30$ /hr (Consensus).

### Testing with Portable Monitors

PM for the diagnosis of OSA should be performed only in conjunction with a comprehensive sleep evaluation. Clinical sleep evaluations using PM must be supervised by a practitioner with board certification in sleep medicine or an individual who fulfills the eligibility criteria for the sleep medicine certification examination (Consensus).<sup>3</sup>

A PM should, at a minimum, record airflow, respiratory effort, and blood oxygenation. The type of biosensors used to monitor these parameters for in-laboratory PSG are recommended for use in PMs and include an oronasal thermal sensor to detect apneas, a nasal pressure transducer to measure hypopneas, oximetry, and, ideally, calibrated or uncalibrated inductance plethysmography for respiratory effort. (Consensus).<sup>3</sup> An experienced sleep technician, sleep technologist, or appropriately trained healthcare practitioner must perform the application of PM sensors or directly educate the patient in the correct application of the sensors (Consensus).<sup>3</sup> PM should be performed under the auspices of an AASM accredited comprehensive sleep medicine program with policies and procedures for sensor application, scoring, and interpretation of the collected data. A quality/performance improvement program for PM including inter-scorer reliability must be in place to assure accuracy and reliability.<sup>3</sup>

PMs may be used in the unattended setting as an alternative to PSG for the diagnosis of OSA in patients with a high pretest probability of moderate to severe OSA and no comorbid sleep disorder or major comorbid medical disorders when all of the previous parameters are met (Consensus).<sup>3</sup> The diagnosis of OSA is confirmed and severity determined using the same criteria as used for PSG. Scoring criteria should be consistent with the current published AASM standards for scoring of apneas and hypopneas (Consensus).<sup>3,9</sup> The term *RDI* has been defined differently when used with PMs than when used with PSG. RDI PM is the number of apneas + hypopneas / total recording time rather than total sleep time.<sup>12</sup> As a result, PMs are likely to underestimate the severity of events compared to the AHI by PSG. Due to the known rate of false negative PM tests, in-laboratory PSG should be performed in cases where PM is technically inadequate or fails to establish the diagnosis of OSA in patients with a high pretest probability (Consensus).<sup>3</sup>

### Other Sleep Procedures

The multiple sleep latency test (MSLT) is not routinely indicated in the initial evaluation and diagnosis of OSA or in an assessment of change following treatment with nasal CPAP. However, if excessive sleepiness continues despite optimal treatment, the patient may require an evaluation for possible narcolepsy, includ-

**Table 5**—Components of Patient Education Programs

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Findings of study, severity of disease
Pathophysiology of OSA
Explanation of natural course of disease and associated disorders
Risk factor identification, explanation of exacerbating factors, and risk factor modification,
Genetic counseling when indicated
Treatment options
What to expect from treatment
Outline the patient's role in treatment, address their concerns, and set goals
Consequences of untreated disease
Drowsy driving/sleepiness counseling
Patient quality assessment and other feedback regarding evaluation

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ing the MSLT (Guideline).<sup>13</sup> Actigraphy alone is not indicated for the routine diagnosis of OSA but may be a useful adjunct to PMs when determining the rest-activity pattern during the testing period (Option).<sup>14</sup> Autotitrating positive airway pressure (APAP) is not recommended to diagnose OSA.<sup>15</sup>

### Patient Education

The sleep specialist should review the results of objective testing with the patient, including education on the nature of the disorder and treatment options (Table 5). The educational program should include discussion of the pathophysiology, risk factors, natural history, and clinical consequences of OSA. Treatment options should be discussed in the context of the severity of the patient's OSA, their risk factors, any associated conditions, and the patient's expectations. General education on the impact of weight loss, sleep position, alcohol avoidance, risk factor modification, and medication effects should be provided. The patient should be counseled on the risks and management of drowsy driving. Patient education should optimally be delivered as part of a multidisciplinary chronic disease management team including the sleep physician, the referring provider, and allied health care providers. In addition, videotapes, handouts, websites, and brochures can be employed (Consensus).

### Treatment

OSA should be approached as a chronic disease requiring long-term, multidisciplinary management. There are medical, behavioral, and surgical options for the treatment of OSA. Adjunctive therapies are used as needed to supplement the primary treatment options. The patient should be an active participant in the decision on treatment type and taught to contribute to the management of his or her own disease. Positive airway pressure (PAP) is the treatment of choice for mild, moderate, and severe OSA and should be offered as an option to all patients (Consensus). Alternative therapies may be offered depending on the severity of the OSA and the patient's anatomy, risk factors, and preferences and should be discussed in detail. (Figure 1)

A general OSA outcomes assessment should be performed on all patients following the initiation of therapy. Outcome indicators to monitor with therapy include: evaluation of resolution of sleepiness (using subjective scales such as the Epworth

**Table 6**—General OSA Outcomes Assessment

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Resolution of sleepiness
OSA specific quality of life measures
Patient and spousal satisfaction
Adherence to therapy
Avoidance of factors worsening disease
Obtaining an adequate amount of sleep
Practicing proper sleep hygiene
Weight loss for overweight/obese patients

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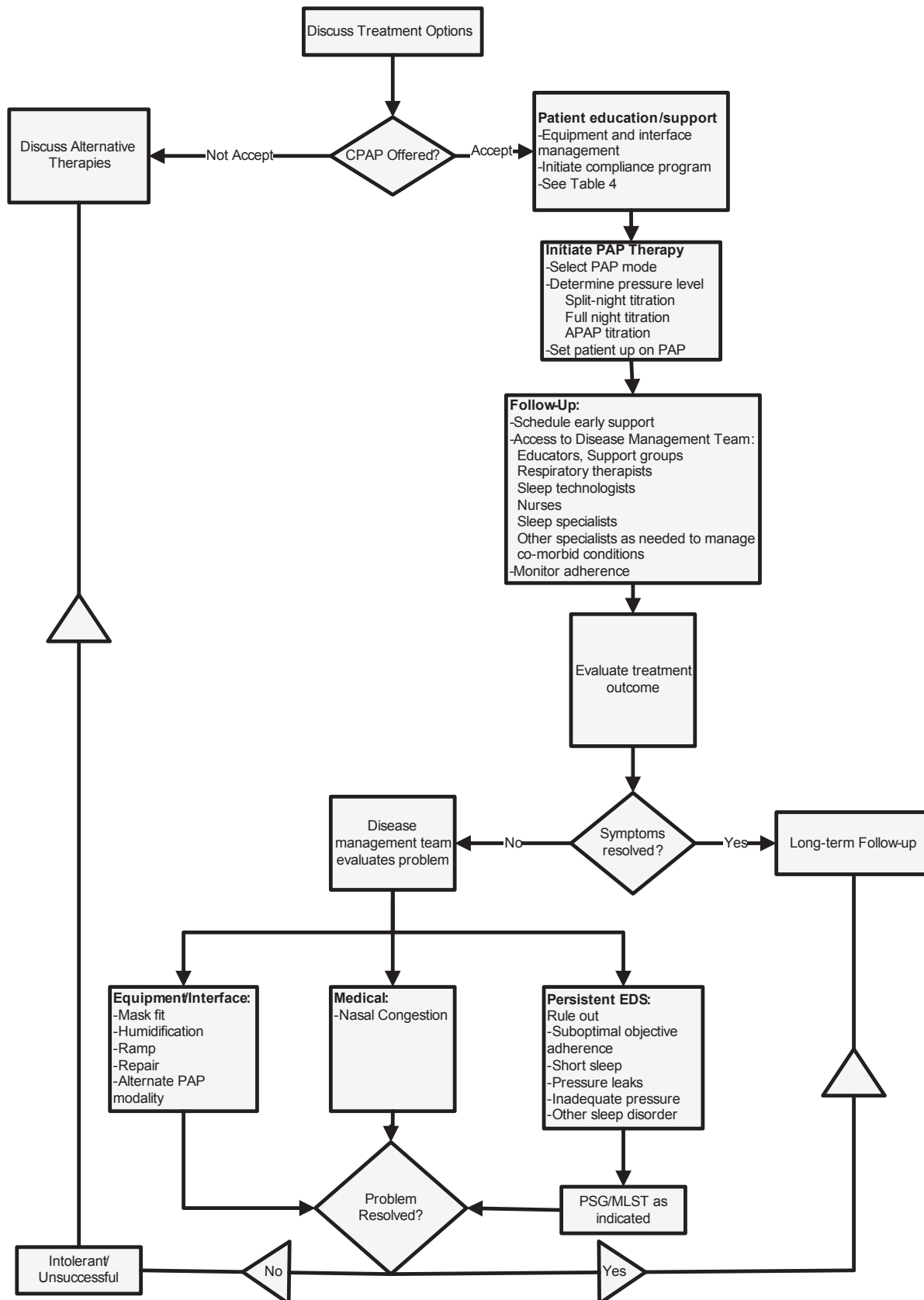
Sleepiness Scale<sup>5</sup> or objective measures such as the multiple sleep latency test or maintenance of wakefulness test if sleepiness persists despite effective treatment), OSA-specific quality of life measures, patient and spousal satisfaction, adherence to therapy, avoidance of factors worsening disease, obtaining an adequate amount of sleep, practicing proper sleep hygiene, and weight loss for overweight/obese patients (Consensus). (Table 6) Additional therapy-specific outcomes should also be assessed as described below.

### POSITIVE AIRWAY PRESSURE

First described by Sullivan in 1981,<sup>16</sup> PAP provides pneumatic splinting of the upper airway and is effective in reducing the AHI.<sup>17</sup> PAP may be delivered in continuous (CPAP), bilevel (BPAP), or autotitrating (APAP) modes. Partial pressure reduction during expiration (pressure relief) can also be added to these modes. PAP applied through a nasal, oral, or oronasal interface during sleep is the preferred treatment for OSA.<sup>17</sup> CPAP is indicated for the treatment of moderate to severe OSA (Standard) and mild OSA (Option).<sup>18</sup> CPAP is also indicated for improving self-reported sleepiness (Standard), improving quality of life (Option), and as an adjunctive therapy to lower blood pressure in hypertensive patients with OSA (Option).<sup>18</sup> The approach to initiation, management, and follow-up of CPAP is summarized in Figure 2.

Full-night, attended PSG performed in the laboratory is the preferred approach for titration to determine the optimal PAP level; however, split-night, diagnostic-titration studies are usually adequate (Guideline).<sup>18</sup> APAP devices are not currently recommended for split-night titration (Standard).<sup>15</sup> Guidelines have recently been published on the method for conducting CPAP and BPAP titrations.<sup>19</sup> Certain APAP devices may be used during attended titration with PSG to identify a single pressure for use with standard CPAP for treatment of moderate to severe OSA (Guideline).<sup>15</sup> Certain APAP devices may be used in an unattended way to determine a fixed CPAP treatment pressure for patients with moderate to severe OSA without significant comorbidities (CHF, COPD, central sleep apnea syndromes, or hypoventilation syndromes) (Option).<sup>15</sup>

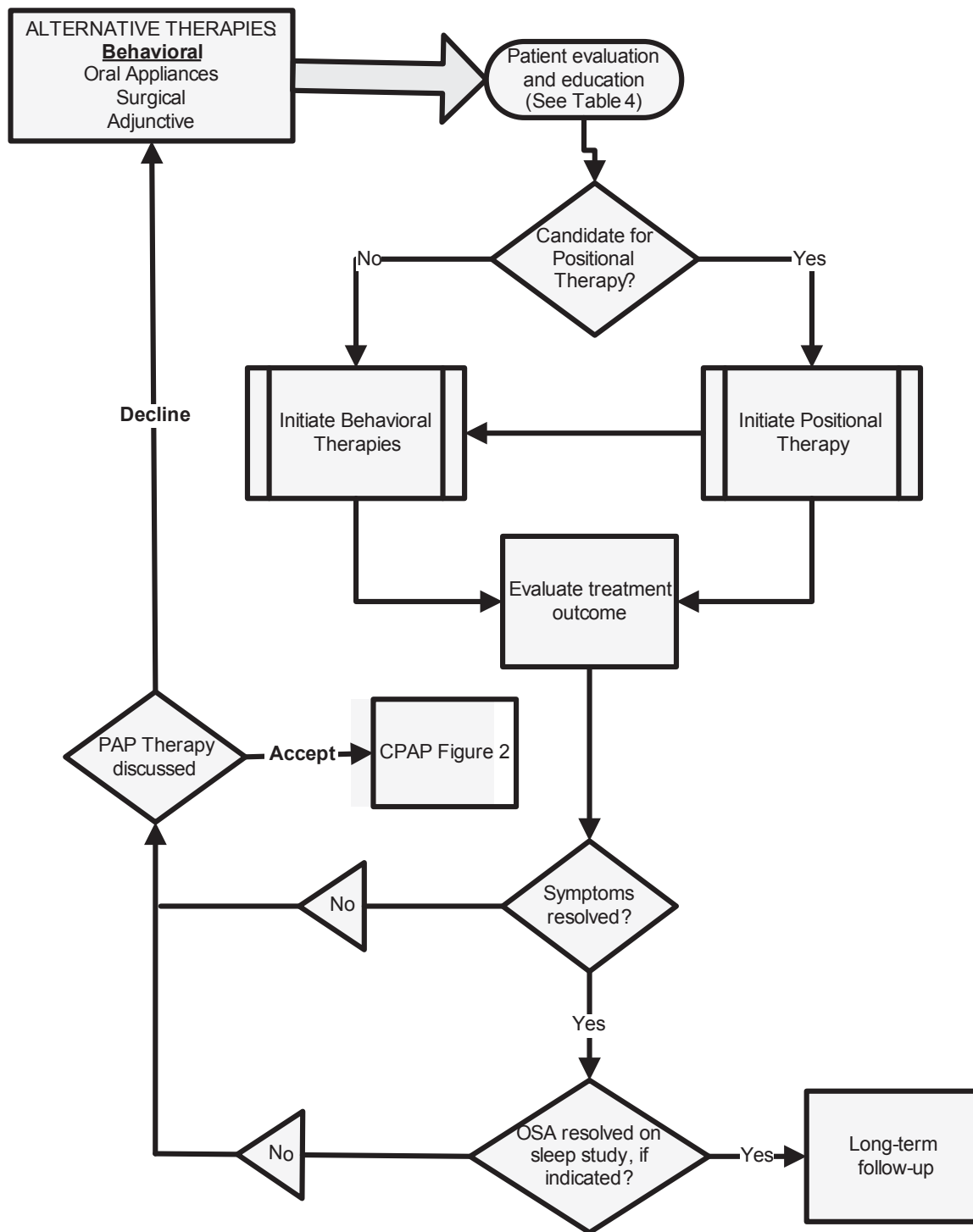
BPAP, pressure relief, or APAP can be considered in the management of OSA in CPAP-intolerant patients (Consensus). While the literature mainly supports CPAP therapy, BPAP is an optional therapy in some cases where high pressure is needed and the patient experiences difficulty exhaling against a fixed pressure or coexisting central hypoventilation is present (Guideline).<sup>18,20</sup> Pressure waveform modification technologies (such as pressure relief) may improve patient comfort and adherence with PAP (Consensus).<sup>19</sup> Certain APAP devices may be initiated



**Figure 2**—CPAP Treatment. Approach to initiation, management, and follow-up of CPAP.

and used in the self-adjusting mode for unattended treatment of patients with moderate to severe OSA without significant comorbidities (CHF, COPD, central sleep apnea syndromes, or hypoventilation syndromes) (Option).<sup>15</sup>

Treatment with PAP should ideally be approached on a case management basis utilizing a multidisciplinary care team that can include a sleep specialist, the referring physician, nursing personnel, respiratory therapist, and sleep technologist.



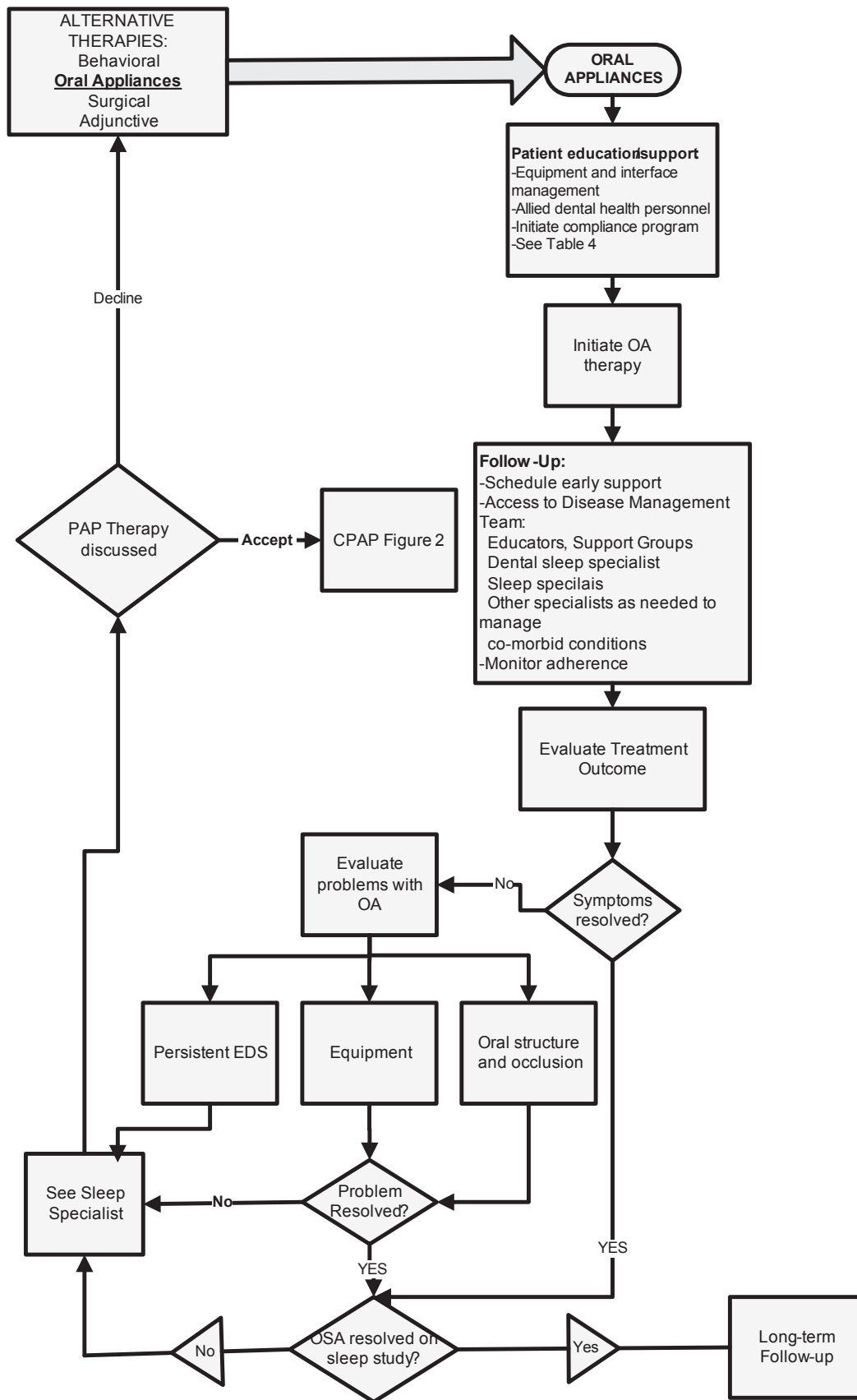
**Figure 3**—Behavioral Treatment. Approach to initiation, management, and follow-up of behavioral treatment.

Patients should be educated about the function, care, and maintenance of their equipment, the benefits of PAP therapy, and potential problems. Patients, in conjunction with their care team, should work together to select the most appropriate PAP interface. The nasal airway is the preferred delivery route, however, alternatives may be tried to accommodate for comfort or difficulties (Consensus). The addition of heated humidification and a systematic educational program is indicated to improve CPAP utilization (Standard).<sup>18</sup> CPAP usage should be objectively monitored with time meters to help assure utilization (Standard).<sup>18</sup> CPAP and BPAP therapy are

safe; side effects and adverse events are mainly minor and reversible (Standard).<sup>18</sup>

Close follow-up for PAP usage and problems by appropriately trained health care providers is indicated to establish effective utilization patterns and remediate problems, if needed. This is especially important during the first few weeks of PAP use (Standard).<sup>18</sup> General OSA outcomes should be assessed in all patients (Consensus) (Table 6). If CPAP use is considered inadequate based on objective monitoring and symptom evaluation, prompt and intensive efforts should be implemented to improve PAP use or consider alternative therapies





**Figure 4**—Oral Appliances. Approach to initiation, management, and follow-up of patients using custom OA therapy.

(Consensus). After initial PAP setup, long-term follow-up by appropriately trained health care providers is indicated yearly and as needed to troubleshoot PAP mask, machine, or usage

problems (Option).<sup>18</sup> The General Outcomes assessment described above and in Table 6 should be performed at follow-up visits.

## BEHAVIORAL STRATEGIES

Behavioral treatment options include weight loss, ideally to a BMI of 25 kg/m<sup>2</sup> or less; exercise; positional therapy; and avoidance of alcohol and sedatives before bedtime. Regardless of behavioral approach, general OSA outcomes should be assessed after initiation of therapy in all patients (Consensus) (Table 6). The approach to initiation, management, and follow-up of behavioral treatment is summarized in Figure 3.

Successful dietary weight loss may improve the AHI in obese patients with OSA (Guideline).<sup>21</sup> Weight loss should be recommended for all overweight OSA patients. Weight loss should be combined with a primary treatment for OSA (Option) because of the low success rate of dietary programs and the low cure rate by dietary approach alone.<sup>21</sup> After substantial weight loss (i.e., 10% or more of body weight), a follow-up PSG is routinely indicated to ascertain whether PAP therapy is still needed or whether adjustments in PAP level are necessary (Standard).<sup>6</sup>

Sleep position can affect airway size and patency with a decrease in the area of the upper airway, particularly in the lateral dimension, while in the supine position.<sup>22</sup> Positional therapy, consisting of a method that keeps the patient in a non-supine position, is an effective secondary therapy or can be a supplement to primary therapies for OSA in patients who have a low AHI in the non-supine versus that in the supine position (Guideline).<sup>21</sup> Because not all patients normalize AHI when non-supine, correction of OSA by position should be documented with PSG before initiating this form of treatment as a primary therapy (Consensus). A positioning device (e.g., alarm, pillow, backpack, tennis ball) should be used when initiating positional therapy (Consensus). To establish the efficacy of a positioning device in the home, providers should consider use of an objective position monitor (Consensus). Treatment specific outcome indicators to monitor with therapy include: self-reported compliance, objective position monitoring, side effects, and symptom resolution (Consensus).

## ORAL APPLIANCES

Custom made oral appliances (OA) may improve upper airway patency during sleep by enlarging the upper airway and/or by decreasing upper airway collapsibility (e.g., improving upper airway muscle tone).<sup>23</sup> Mandibular repositioning appliances (MRA) cover the upper and lower teeth and hold the mandible in an advanced position with respect to the resting position. Tongue retaining devices (TRD) hold only the tongue in a forward position with respect to the resting position, without mandibular repositioning. An approach to initiation, management, and follow-up of patients using custom OA therapy is summarized in Figure 4.

Although not as efficacious as CPAP, OAs are indicated for use in patients with mild to moderate OSA who prefer OAs to CPAP, or who do not respond to CPAP, are not appropriate candidates for CPAP, or who fail CPAP or behavioral measures such as weight loss or sleep position change (Guideline).<sup>4</sup> OAs are appropriate for use in patients with primary snoring who do not respond to, or are not appropriate candidates for, treatment with behavioral measures such as weight loss or sleep position change (Guideline).<sup>4</sup> Patients with severe OSA should have an

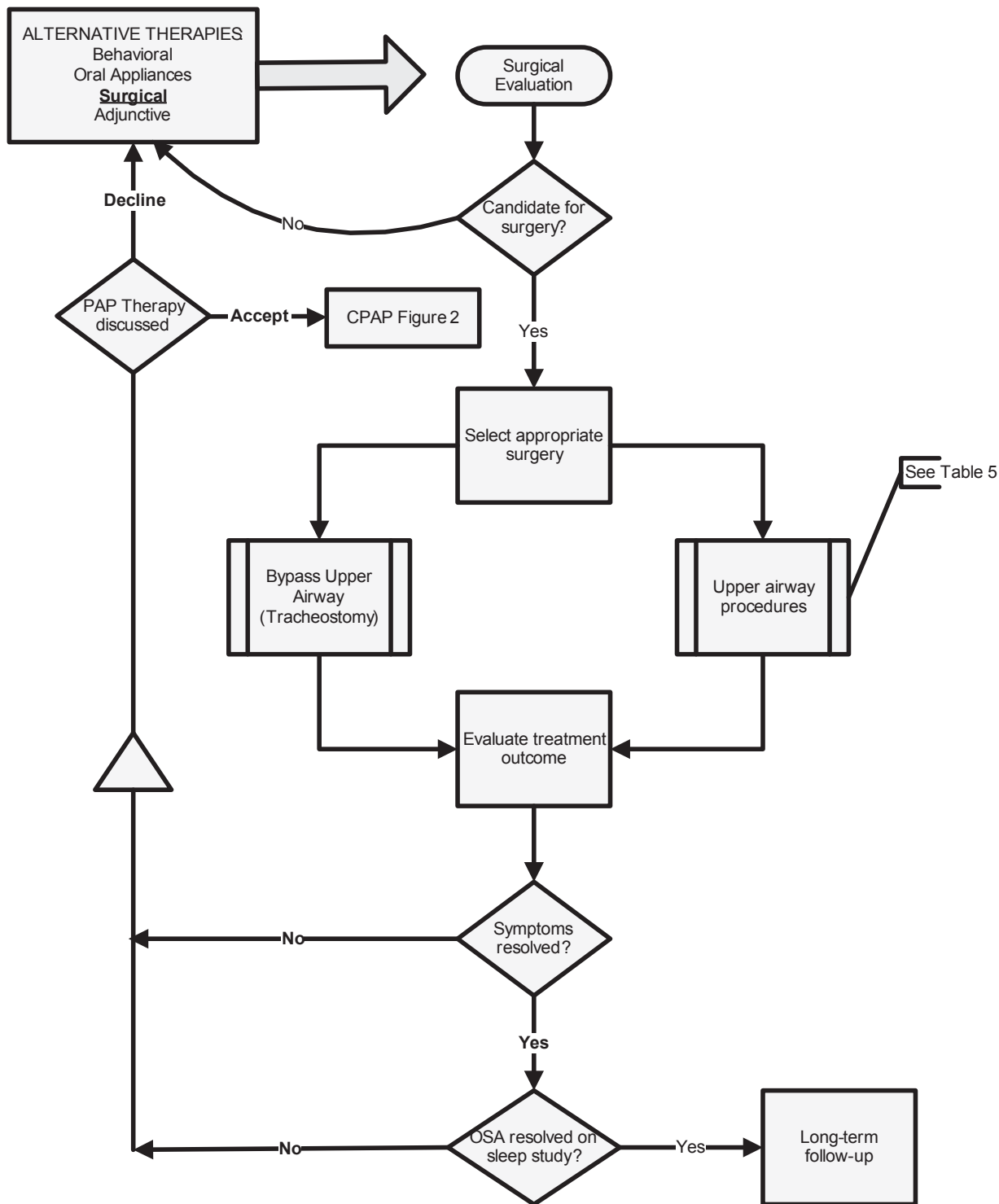
initial trial of nasal CPAP because greater effectiveness has been shown with this intervention than with the use of OAs. Upper airway surgery (including tonsillectomy and adenoidectomy, craniofacial operations, and tracheostomy) may also supersede use of OAs in patients for whom these operations are predicted to be highly effective in treating sleep apnea (Guideline).<sup>4</sup>

The presence or absence of OSA must be determined before initiating treatment with OAs to identify those patients at risk due to complications of sleep apnea and to provide a baseline to establish the effectiveness of subsequent OA treatment. The severity of sleep related respiratory problems must be established in order to make an appropriate treatment decision (Standard).<sup>4</sup>

Patients should undergo a thorough dental examination to assess candidacy for an OA. The evaluation should include a dental history and complete intra-oral examination. This examination includes a soft tissue, periodontal and temporomandibular joint (TMJ) assessment, an appraisal for characteristic patterns of wear from nocturnal bruxism, and evaluation of occlusion.<sup>23</sup> Dental records should be reviewed, and dental radiographs or a panorex survey may be obtained to assess for possible dental pathology.<sup>23</sup> Although a cephalometric evaluation is not always required for patients who will use an OA, appropriately trained professionals should perform cephalometric examinations when they are deemed necessary (Option).<sup>4</sup> Oral appliances should be fitted by qualified dental personnel who are trained and experienced in the overall care of oral health, the temporomandibular joint, dental occlusion, and associated oral structures. Dental management of patients with OAs should be overseen by practitioners who have undertaken serious training in sleep medicine and/or sleep related breathing disorders with focused emphasis on the proper protocol for diagnosis, treatment, and follow-up of OSA while using an OA (Option).<sup>4</sup>

Candidates for a MRA require adequate healthy teeth upon which to seat the oral appliance, no important TMJ disorder, adequate jaw range of motion, and adequate manual dexterity and motivation to insert and remove the OA, as determined by a qualified dental professional (Consensus). TRDs may be used at any phase of treatment but may be useful when the patient lacks the prerequisites for treatment with MRAs (Consensus). Intolerance and improper use of the device are potential problems for patients using OAs, which require patient effort to use properly. OAs may aggravate TMJ disease and may cause dental misalignment and discomfort that are unique to each device. In addition, OAs can be rendered ineffective by patient alteration of the device (Option).

For patients with OSA, the desired outcome of treatment includes the resolution of the clinical signs and symptoms of OSA and the normalization of the apnea-hypopnea index and oxyhemoglobin saturation (Standard).<sup>4</sup> General OSA outcomes should be assessed in all patients (Consensus) (Table 6). OAs should be monitored shortly after initiation of treatment and then as frequently as needed in order to assure patient accommodation, comfort, adequate device titration, and adherence, and to assess symptoms and side effects (Consensus). To ensure satisfactory therapeutic benefit from OAs, patients with OSA should undergo PSG or an attended cardiorespiratory (type 3) sleep study with the oral appliance in place after final adjustments of fit have been performed (Guideline).<sup>4</sup> Additionally,



**Figure 5**—Surgical Treatment. Approach to the management of OSA with surgical therapy.

unattended PM may be indicated to monitor the response to non-CPAP treatments for OSA, including OAs (Consensus).<sup>3</sup> Once optimal fit is obtained and efficacy shown, follow-up with a dental specialist is recommended every 6 months for the first year, and at least annually thereafter. The purpose of follow-up is to monitor patient adherence, evaluate device deterioration or maladjustment, evaluate the health of the oral structures and integrity of the occlusion, and assess the patient for signs and symptoms of worsening OSA. During all phases of assessment, therapy, and follow-up, patients should have access to a

care team with appropriate dental personnel, educators, support groups, and sleep specialists (Consensus).

**SURGICAL TREATMENT**

The first methods used to treat OSA were surgical. Surgical therapy includes a variety of upper airway reconstructive or bypass procedures, often site-directed and/or staged (Consensus). A list of common surgical procedures for OSA is given in Table 7. The specifics of sleep apnea surgery are beyond the scope of

**Table 7**—Common Surgical Procedures for OSA by Site

Upper Airway Bypass Procedure	Tracheotomy
Nasal Procedures	Septoplasty Functional rhinoplasty Nasal valve surgery Turbinate reduction Nasal polypectomy Endoscopic procedures
Oral, Oropharyngeal, and Nasopharyngeal Procedures	Uvulopalatopharyngoplasty and variations Palatal advancement pharyngoplasty Tonsillectomy and/or adenoidectomy Excision of tori mandibularis Palatal implants
Hypopharyngeal Procedures	Tongue Reduction Partial glossectomy Tongue ablation Lingual tonsillectomy Tongue Advancement/Stabilization Genioglossus advancement Hyoid suspension Mandibular advancement Tongue suspension
Laryngeal Procedures	Epiglottoplasty Hyoid suspension
Global Airway Procedures	Maxillomandibular advancement Bariatric surgery

this guideline. A general approach to the management of OSA with surgical therapy is summarized in Figure 5.

This guideline does not apply to surgical therapy for primary snoring.

The diagnosis of OSA should be established prior to surgery and the severity determined by objective testing (Consensus). In addition to the general sleep evaluation described above, patients should be evaluated for eligibility for surgery. This evaluation should include an anatomical examination to identify possible surgical sites, an assessment of any medical, psychological or social comorbidities that might affect surgical outcome, and a determination of the patient's desire for surgery (Consensus). The patient should be counseled on the surgical options, likelihood of success, goals of treatment, risks and benefits of the procedure, possible side effects, and complications and alternative treatments (Consensus).

Evaluation for primary surgical treatment can be considered in patients with mild OSA who have severe obstructing anatomy that is surgically correctible (e.g., tonsillar hypertrophy obstructing the pharyngeal airway) (Consensus). Surgical procedures may be considered as a secondary treatment for OSA when the outcome of PAP therapy is inadequate, such as when the patient is intolerant of PAP, or PAP therapy is unable to eliminate OSA (Consensus). Surgery may also be considered as a secondary therapy when there is an inadequate treatment outcome with an OA, when the patient is intolerant of the OA, or the OA therapy provides unacceptable improvement of clinical outcomes of OSA (Consensus). Surgery may also be considered as an adjunct therapy when obstructive anatomy or functional

deficiencies compromise other therapies or to improve tolerance of other OSA treatments (Consensus).

Tracheostomy can eliminate OSA but does not appropriately treat central hypoventilation syndromes (Consensus). Maxillary and mandibular advancement can improve PSG parameters comparable to CPAP in the majority of patients (Consensus). Most other sleep apnea surgeries are rarely curative for OSA but may improve clinical outcomes (e.g., mortality, cardiovascular risk, motor vehicle accidents, function, quality of life, and symptoms) (Consensus). Laser-assisted uvulopalatoplasty is not recommended for the treatment of obstructive sleep apnea (Guideline).<sup>24</sup>

The frequency of post-surgical follow-up will be determined by the type of surgery but should include a surgery-specific evaluation as well a general OSA-related evaluation. Surgery specific outcomes to be evaluated by the surgical team include wound healing, assessment of anatomical result, side effects, and complications (Consensus). For patients undergoing multi-step procedures, sleep specialist evaluation may be considered between surgeries for an intermediate sleep study to assess response or reconsideration of all non-surgical therapies, if indicated. After the surgical team determines healing is completed, a final general OSA outcome evaluation is indicated (Consensus) (Table 6). Sleep specialist follow-up is recommended for long-term follow-up after surgical treatment is completed (Consensus). Following adjunctive surgery, patients should be evaluated to assess the effect of surgery on PAP or OA tolerance, adherence, and symptom resolution (Consensus).

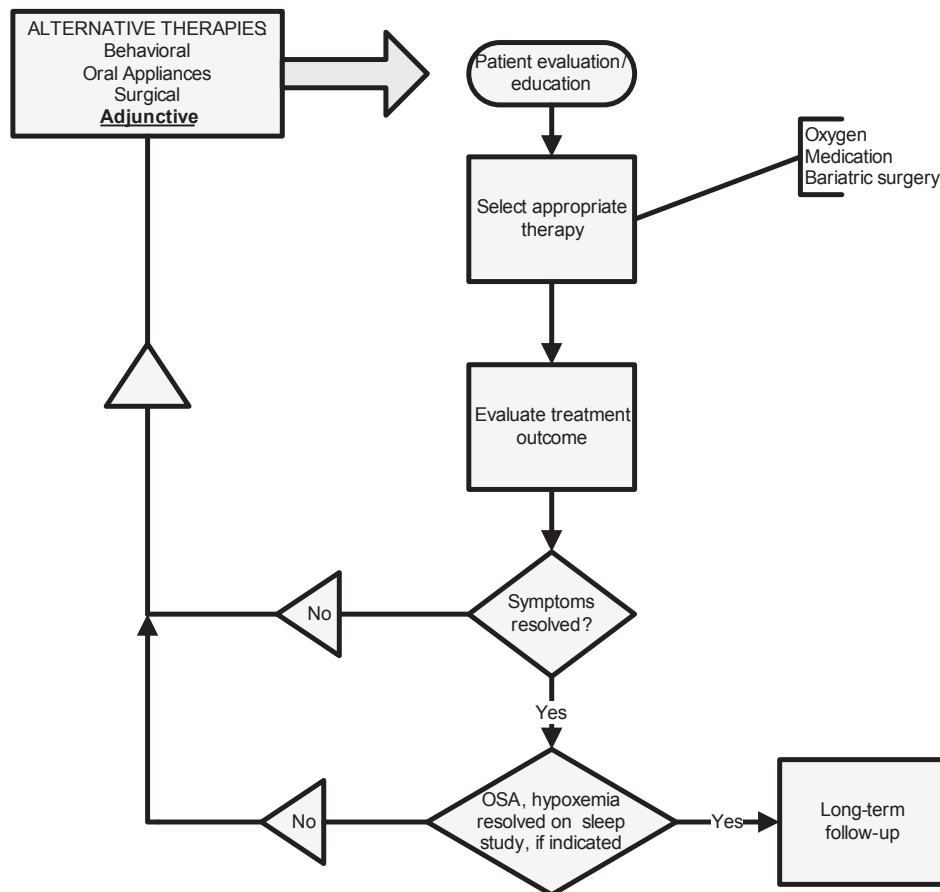
## Adjunctive Therapies

### BARIATRIC SURGERY

Bariatric surgery is an effective means to achieve major weight loss and is indicated in individuals with a body mass index (BMI)  $\geq 40$  kg/m<sup>2</sup> or those with a BMI  $\geq 35$  kg/m<sup>2</sup> with important comorbidities and in whom dietary attempts at weight control have been ineffective.<sup>25</sup> Bariatric surgery may be adjunctive in the treatment of OSA in obese patients (Option).<sup>21</sup> Bariatric surgery should be considered as an adjunct to less invasive and rapidly active first-line therapies such as PAP for patients who have OSA and meet the currently published guidelines for bariatric surgery (Consensus). The remission rate for OSA two years after bariatric surgery, related to the amount of weight lost, is 40%, emphasizing the need for ongoing clinical follow-up of these patients.<sup>26</sup>

### PHARMACOLOGIC AGENTS AND OXYGEN THERAPY

There are no widely effective pharmacotherapies for OSA with the important exceptions of individuals with hypothyroidism or acromegaly. Treatment of those underlying medical conditions can improve the AHI.<sup>27</sup> Specifically, selective serotonergic uptake inhibitors (SSRIs) (Standard), protriptyline (Guideline), methylxanthine derivatives (aminophylline and theophylline) (Standard), and estrogen therapy (estrogen preparations with or without progesterone) (Standard) are not recommended for the treatment of OSA.<sup>21</sup> Short-acting nasal decongestants are not recommended for treatment of OSA (Option), but topical nasal



**Figure 6**—Adjunctive Treatment. Approach to the management of OSA with adjunctive therapies

corticosteroids may improve the AHI in patients with OSA and concurrent rhinitis, and thus may be a useful adjunct to primary therapies for OSA (Guideline).<sup>21</sup>

Oxygen supplementation is not recommended as a primary treatment for OSA (Option).<sup>21</sup> If supplemental oxygen is used as an adjunct to other primary therapies to treat hypoxemia, follow-up must include documentation of resolution of the hypoxemia (Consensus). Supplemental oxygen alone may reduce nocturnal hypoxemia but may also prolong apneas and may potentially worsen nocturnal hypercapnia in patients with comorbid respiratory disease.<sup>28</sup>

Modafinil is recommended for the treatment of residual excessive daytime sleepiness in OSA patients who have sleepiness despite effective PAP treatment and who are lacking any other identifiable cause for their sleepiness (Standard).<sup>21</sup> Before using modafinil, other causes of residual sleepiness must be ruled out including: suboptimal objective adherence with PAP; ill-fitting PAP masks; insufficient sleep; poor sleep hygiene; other sleep disorders such as narcolepsy or restless legs syndrome/periodic limb movements of sleep; and depression. Modafinil should be used in addition to PAP therapy. An approach to the management of OSA with adjunctive therapies is summarized in Figure 6.

### Special Populations

In certain special populations the acceptance of routine care of OSA may be difficult and requires close discussion with pa-

tients, families, and clinicians to formulate a well tolerated care program. Patients with Down syndrome, Alzheimer disease, and mental and physical handicaps may find any given therapy for OSA difficult. Clinical judgment is needed to determine what degree of care for OSA is acceptable to the patient and achievable as a long-term care plan.

### Long-Term Management

All patients with OSA should have ongoing, long-term management for their chronic disorder. Those on chronic therapy (PAP, OA, positional therapy) should have regular, ongoing follow-up to monitor adherence to therapy, side effects, development of medical complications related to OSA, and continued resolution of symptoms. Those with elimination of OSA (weight loss, surgery) should be monitored for continued risk factor modification and to look for return of symptoms.

### Conclusion

In 1999 the Institutes of Medicine recommended that professional societies raise the standard of practice, improve clinical outcomes, and improve patient safety by developing practice guidelines.<sup>29</sup> This clinical guideline brings together the recommendations from the evidence-based practice parameters of the American Academy of Sleep Medicine along with best practice consensus recommendations from clinician experts where evidence-based guidelines do not yet exist. Practitioners should

use this guideline as a template for developing a comprehensive treatment program for patients with OSA. The guideline will be updated as further evidence becomes available.

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### REFERENCES

- American Academy of Sleep Medicine. International classification of sleep disorders, 2nd Edition: Diagnostic and coding manual. Westchester, IL: American Academy of Sleep Medicine; 2005.
- Delbecq A, vande Ven A. A group process model for problem identification and programme planning. *J Appl Behav Sci* 1971;7:467-92.
- Collop NA, Anderson WM, Boehlecke B, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2007;3:737-47.
- Kushida CA, Morgenthaler TI, Littner MR, et al. Practice parameters for the treatment of snoring and Obstructive Sleep Apnea with oral appliances: an update for 2005. *Sleep* 2006;29:240-3.
- Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-5.
- Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep* 2005;28:499-521.
- Friedman M, Tanyeri H, La Rosa M, et al. Clinical predictors of obstructive sleep apnea. *Laryngoscope* 1999;109:1901-7.
- Littner M, Hirshkowitz M, Davila D, et al. Practice parameters for the use of auto-titrating continuous positive airway pressure devices for titrating pressures and treating adult patients with obstructive sleep apnea syndrome. An American Academy of Sleep Medicine report. *Sleep* 2002;25:143-7.
- Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
- American Academy of Sleep Medicine. Standards for Accreditation. Westchester: American Academy of Sleep Medicine; 2007.
- Center for Medicare and Medicaid Services. In: Department of Health and Human Services, ed. Supplementary Medical Insurance (SMI) Benefits. 42 CFR 410.33.
- Trikalinos TA, Lau J. Obstructive Sleep Apnea-Hypopnea Syndrome: modeling different diagnostic strategies. Rockville, MD: AHRQ Technology Assessment Program; U.S. Dept Health Human Services; Agency for Healthcare Research and Quality; 2007.
- Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep* 2005;28:113-21.
- Morgenthaler T, Alessi C, Friedman L, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. *Sleep* 2007;30:519-29.
- Morgenthaler TI, Aurora RN, Brown T, et al. Practice parameters for the use of autotitrating continuous positive airway pressure devices for titrating pressures and treating adult patients with obstructive sleep apnea syndrome: an update for 2007. An American Academy of Sleep Medicine report. *Sleep* 2008;31:141-7.
- Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* 1981;1:862-5.
- Gay P, Weaver T, Loube D, Iber C. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. *Sleep* 2006;29:381-401.
- Kushida CA, Littner MR, Hirshkowitz M, et al. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. *Sleep* 2006;29:375-80.
- Kushida CA, Chediak A, Berry RB, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. *J Clin Sleep Med* 2008;4:157-71.
- Ballard RD, Gay PC, Strollo PJ. Interventions to improve compliance in sleep apnea patients previously non-compliant with continuous positive airway pressure. *J Clin Sleep Med* 2007;3:706-12.
- Morgenthaler TI, Kapen S, Lee-Chiong T, et al. Practice parameters for the medical therapy of obstructive sleep apnea. *Sleep* 2006;29:1031-5.
- Pevernagie DA, Stanson AW, Sheedy PF 2nd, Daniels BK, Shepard JW Jr. Effects of body position on the upper airway of patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1995;152:179-85.
- Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. *Sleep* 2006;29:244-62.
- Littner M, Kushida CA, Hartse K, et al. Practice parameters for the use of laser-assisted uvulopalatoplasty: an update for 2000. *Sleep* 2001;24:603-19.
- SAGES Guidelines Committee. Guidelines for clinical application of laparoscopic bariatric surgery: Society of American Gastrointestinal and Endoscopic Surgeons; 2008.
- Mechanick JI, Kushner RF, Sugerman HJ, et al. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery Medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. *Endocr Pract* 2008;14 Suppl 1:1-83.
- Veasey SC, Guilleminault C, Strohl KP, Sanders MH, Ballard RD, Magalang UJ. Medical therapy for obstructive sleep apnea: a review by the Medical Therapy for Obstructive Sleep Apnea Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. *Sleep* 2006;29:1036-44.
- Berry RB, Light RW. Effect of hyperoxia on the arousal response to airway occlusion during sleep in normal subjects. *Am Rev Respir Dis* 1992;146:330-4.
- Kohn L, Corrigan JM, Donaldson MS. To Err is Human. Washington, DC: Institute of Medicine, National Academy Press; 1999.