



(<https://www.aetna.com/>)

Obstructive Sleep Apnea in Adults

[Clinical Policy Bulletins](#) | [Medical Clinical Policy Bulletins](#)

Number: 0004

Table Of Contents

[Policy](#)

[Applicable CPT / HCPCS / ICD-10 Codes](#)

[Background](#)

[References](#)

Policy

[Scope of Policy](#)

This Clinical Policy Bulletin addresses diagnostic and treatment modalities and associated accessories and supplies for obstructive sleep apnea in adults.

Policy History

[Last Review](#) 02/08/2024

Effective: 08/10/1995

Next Review: 01/11/2024

[Review History](#)

[Definitions](#)

Additional Information

[Clinical Policy Bulletin Notes](#)

Top

I. Medical Necessity

A. Diagnosis

Aetna considers the following tests medically necessary for diagnosing obstructive sleep apnea (OSA) in adults aged 18 years and older when criteria are met:

1. Attended Full-Channel Nocturnal Polysomnography (NPSG)

Attended full-channel nocturnal polysomnography (NPSG) (Type I device) performed in a healthcare facility is considered medically necessary for diagnosis in members with symptoms suggestive of obstructive sleep apnea (see [Appendix](#)), when attended NPSG is used as part of a comprehensive sleep evaluation with adequate followup, and member has one or more of the following indications for attended NPSG:

- a. Member has *at least one* of the following comorbid medical conditions that degrade the accuracy of portable monitoring:
 - i. moderate to severe pulmonary disease (for example, COPD or asthma) (with nocturnal oxygen use or daytime hypercapnia with documented arterial blood gasses showing pO₂ less than 60 or pCO₂ greater than 45),
 - ii. neuromuscular disease (e.g., Parkinson's disease, spina bifida, myotonic dystrophy, amyotrophic lateral sclerosis),
 - iii. stroke with residual respiratory effects,
 - iv. epilepsy,
 - v. congestive heart failure (NYHA class III or IV or LVEF less than 45%),
 - vi. pulmonary hypertension (mean pulmonary artery pressure > 25 mm Hg),
 - vii. chronic opioid medication use,
 - viii. super obesity (BMI greater than 45, or pulmonary function studies show obesity hypoventilation syndrome (BMI greater than 35 plus arterial blood

gas with PCO₂ greater than 45, or BMI greater than 35 plus inability to lie flat in bed)); *or*

b. Member has *one or more* of the following comorbid sleep disorders:

- i. periodic limb movement disorder (involuntary, jerking movements of the legs during sleep causing excessive daytime sleepiness (EDS) due to sleep fragmentation),
 - ii. parasomnias that are unusual or atypical because of the individual's age at onset, the time, duration or frequency of occurrence of the behavior including, but not limited to: nocturnal seizures, psychogenic dissociative states, REM sleep behavior disorder, sleep talking and/or confusional arousals,
 - iii. severe insomnia,
 - iv. narcolepsy,
 - v. central sleep apnea or complex sleep apnea; *or*
- c. Member has negative or technically inadequate portable monitoring results; *or*
- d. Member has low pretest probability of obstructive sleep apnea (normal BMI (less than 30), normal airway (Mallampati score 1 or 2), no snoring, and normal neck circumference (less than 17 inches in men, and less than 16 inches in women)); *or*
- e. Member lacks the mobility or dexterity to use portable monitoring equipment safely at home.

Aetna considers attended full-channel nocturnal polysomnography (NPSG) (Type I device) performed in a healthcare facility medically necessary for members meet criteria for implantation of the Inspire System.

Note: Where attended NPSG is indicated, a split-night study NPSG is considered medically necessary, in which the final portion of the NPSG is used to titrate continuous positive airway pressure (CPAP), if the Apnea Hypopnea Index (AHI) is greater than 15 in first 2 hours of a diagnostic sleep study. An additional full-night

CPAP titration NPSG is considered medically necessary only if the AHI is less than or equal to 15 during the first 2 hours of a diagnostic sleep study, or if the split-night study did not allow for the abolishment of the vast majority of obstructive respiratory events (see section I.B. below).

2. Unattended (Home) Sleep Studies

Unattended (home) sleep studies using *any* of the following diagnostic techniques (see [Appendix](#) for definition of device types) are considered medically necessary for members with symptoms suggestive of OSA (see [Appendix](#)) when the home sleep study is used as part of a comprehensive sleep evaluation:

- a. Sleep monitoring using a Type II device; *or*
- b. Sleep monitoring using a Type III device, *or*
- c. Sleep monitoring using a Type IV(A) device, measuring airflow and at least 2 other channels and providing measurement of apnea-hypopnea index (AHI); *or*
- d. Sleep monitoring using a device that measures 3 or more channels that include pulse oximetry, actigraphy, and peripheral arterial tone (e.g., Watch-PAT device).

Note: Sleep studies using devices that do not provide a measurement of apnea-hypopnea index (AHI) and oxygen saturation are considered not medically necessary because they do not provide sufficient information to prescribe treatment. Examples include the Biancamed SleepMinder, SNAP testing with fewer than three channels, and the SleepImage Sleep Quality Screener. Note that the ApneaLink does not meet criteria as a covered type IV device because it does not measure airflow; however, the ApneaLink Plus records 5 channels, including airflow, and meets criteria for a covered sleep study device.

Repeat home sleep testing on multiple consecutive nights has no proven value.

B. Other Testing Indications

1. Attended full-channel nocturnal polysomnography (NPSG) (Type I device) performed in a healthcare facility is considered medically necessary for persons diagnosed with obstructive sleep apnea who have *any* of the following indications for attended NPSG:

- a. To titrate CPAP in persons diagnosed with clinically significant OSA for whom in-laboratory NPSG was medically necessary, but who were unable to undergo a split-night study because they had an insufficient AHI (less than 15) during the first two hours of an attended NPSG; *or*
- b. To titrate CPAP in persons with clinically significant OSA for whom in-laboratory NPSG was medically necessary, and who underwent a split-night study that did not abolish the vast majority of obstructive respiratory events; *or*
- c. To monitor results from CPAP in persons with OSA who have persistent significant symptoms (disturbed sleep with significant arousals) despite documented AHI less than 5 on CPAP and documented compliance with CPAP (CPAP used for 70 percent of nights for four or more hours per night, for two or more months); *or*
- d. To confirm diagnosis of obstructive sleep apnea prior to surgical modifications of the upper airway.

2. Video-EEG-NPSG (NPSG with video monitoring of body positions and extended EEG channels) is considered medically necessary to assist with the diagnosis of paroxysmal arousals or other sleep disruptions that are thought to be seizure related when the initial clinical evaluation and results of a standard EEG are inconclusive.

3. SNAP testing using 3 or more channels is considered a medically necessary method of home sleep testing; SNAP testing using less than 3 channels is considered experimental and investigational. See [CPB 0336 Acoustic Pharyngometers and SNAP Testing System \(./300_399/0336.html\)](#).

C. Repeat Sleep Study Indications

It may be necessary to perform repeat sleep studies up to twice a year for *any* of the following indications. **Note:** Where repeat testing is indicated, attended full-channel nocturnal polysomnography (NPSG) (Type I device) performed in a healthcare facility is considered medically necessary for persons who meet criteria for attended NPSG in section I.A. above; in all other cases, unattended (home) sleep studies are considered medically necessary:

1. To determine whether positive airway pressure treatment (i.e., CPAP, bilevel positive airway pressure (BiPAP), demand positive airway pressure (DPAP), variable positive airway pressure (VPAP), or auto-titrating positive airway pressure (AutoPAP)) continues to be effective in persons with new or persistent symptoms, after interrogation of current positive airway pressure device; *or*
2. To determine whether positive airway pressure treatment settings need to be changed in persons with new or persistent symptoms, after interrogation of current positive airway pressure device. (**Note:** This criterion does not apply to AutoPAP devices, as these devices are automatically titrated and do not require manual adjustment of treatment settings.); *or*
3. For persons with substantial weight loss (loss of 10 percent or more body weight) or some other change in their medical condition that would affect the need for continued positive airway pressure treatment (e.g., heart attack, stroke, heart failure), to determine whether continued treatment with positive airway pressure treatment is necessary; *or*
4. To assess treatment response after upper airway surgical procedures and after initial treatment with oral appliances.

Note: A home sleep study is performed over multiple nights with a single interpretation is considered a single sleep study for purposes of reimbursement.

Note: Repeat sleep testing (home or attended sleep studies) for persons getting replacement CPAP equipment is considered not medically necessary unless the member also has one of the indications for repeat testing listed above.

D. *Treatment*

Treatment of snoring alone, without significant OSA, is *not* considered medically necessary.

1. Continuous Positive Airway Pressure (CPAP)

It is expected that members receive lifestyle advice where applicable (i.e., helping people to lose weight, stop smoking and/or decrease alcohol consumption).

- a. Aetna considers CPAP, CPAP with pressure relief technology (eg, C-Flex, C-Flex +) autoPAP (APAP), and APAP with pressure relief technology (eg, A-Flex) medically necessary DME for members with a positive facility-based NPSG *, or with a positive home sleep test^{*} including Type II, III, IV(A) or Watch-PAT devices, as defined by *either* of the following criteria:
 - i. Member's apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) is greater than or equal to 15 events/hour with a minimum of 30 events; *or*
 - ii. AHI or RDI greater than or equal to 5 and less than 15 events/hour with a minimum of 10 events and at least one of the following is met:
 - a. Documented history of stroke; *or*
 - b. Documented hypertension (systolic blood pressure greater than 140 mm Hg and/or diastolic blood pressure greater than 90 mm Hg); *or*
 - c. Documented ischemic heart disease; *or*
 - d. Documented symptoms of impaired cognition, mood disorders, or insomnia; *or*
 - e. Excessive daytime sleepiness (documented by either Epworth greater than 10 (see [Appendix](#))); *or*
 - f. Greater than 20 episodes of oxygen desaturation (i.e., oxygen saturation of less than 85 %) during a full night sleep study, or any one episode of oxygen desaturation (i.e., oxygen saturation of less than 70 %).

*The sleep study is based on a minimum of 2 hours of continuous recorded sleep or shorter periods of continuous recorded sleep if the total number of recorded events during that shorter period is at least the number of events that would have been required in a 2-hour period. If the AHI or RDI is calculated based on less than 2 hours of sleep or recording time, the total number of recorded events used to calculate the AHI or RDI (respectively) must be at least the number of events that would have been required in a 2-hour period (i.e., must reach more than 30 events without symptoms or more than 10 events with symptoms). Projections of AHI or RDI based upon shorter testing times and/or fewer events are not acceptable for use in determining whether the member meets medical necessity criteria. In addition, estimates of AHI or RDI should include all stages of sleep. Estimates of AHI or RDI that only count events during periods of REM sleep (and exclude periods of non-REM sleep from the calculation) are not acceptable for use in determining whether the member meets medical necessity criteria.

Notes: For purposes of this policy, apnea is defined as a cessation of airflow for at least 10 seconds. Hypopnea is defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30 % reduction in thoraco-abdominal movement or airflow as compared to baseline, and with at least a 4 % oxygen desaturation.

The apnea-hypopnea index (AHI) is equal to the average number of episodes of apnea and hypopnea per hour of sleep without the use of a positive airway pressure device. Sleep time can only be measured in a Type I (facility-based polysomnogram) or Type II sleep study. Thus the AHI is reported only in Type I or Type II sleep studies.

The respiratory disturbance index (RDI) is equal to the episodes of apnea and hypopnea per hour of recording without the use of a positive airway pressure device. The RDI is reported in Type III, Type IV, and other home sleep studies.

Leg movement, snoring, respiratory effort related arousals (RERAs), and other sleep disturbances that may be included by some polysomnographic facilities are not considered to meet the AHI and/or RDI definition in this policy.

Although AHI and RDI have been used interchangeably, some facilities use the term RDI to describe a calculation that includes these other sleep disturbances. Requests for positive airway pressure devices will be considered not medically necessary if based upon an index that does not score apneas and hypopneas separately from other sleep disturbance events. Only persons with an AHI and/or RDI, as defined in this policy that meets medical necessity criteria may qualify for a positive airway pressure device.

b. BiPAP without a backup rate feature, BiPAP with pressure relief technology (Bi-Flex), DPAP, VPAP are considered medically necessary DME for members who are intolerant to CPAP or AutoPAP, or for whom CPAP or AutoPAP is ineffective. Ineffective is defined as documented failure to meet therapeutic goals using CPAP or AutoPAP during the titration portion of a facility-based study or during home use despite optimal therapy (i.e., proper mask selection and fitting and appropriate pressure settings). The records must document that both of the following medical necessity criteria are met:

- i. An appropriate interface for the CPAP and AutoPAP has been properly fit and the member is using it without difficulty; *and*
- ii. The current pressure setting of the CPAP or AutoPAP prevents the member from tolerating the therapy and lower pressure settings of the CPAP or AutoPAP were tried but failed to:
 - a. Adequately control the symptoms of OSA; *or*
 - b. Improve sleep quality; *or*
 - c. Reduce the AHI/RDI to acceptable levels.

These alternatives to CPAP may also be considered medically necessary for OSA members with concomitant breathing disorders, which include restrictive thoracic disorders, COPD, and nocturnal hypoventilation. An oral

pressure appliance (OPAP) is considered medically necessary DME only on an exception basis for members who are unable to tolerate a standard nasal/face mask due to facial discomfort, sinus pain, or claustrophobia from masks.

Replacement of positive airway pressure devices is considered medically necessary at the end of their 5-year reasonable useful lifetime (RUL).

Replacement of these items is considered medically necessary prior to the end of the 5-year RUL due to a change in the member's condition.

Replacement needed due to misuse or abuse are not covered.

2. Continued Medical Necessity of Positive Airway Pressure Devices Beyond Initial Authorization Period

Continued use of a positive airway pressure device beyond the initial authorization period is considered medically necessary if the treating physician documents that the member is benefiting from positive airway pressure therapy. Documentation of clinical benefit is demonstrated by:

- a. Face-to-face clinical reevaluation by the treating physician with documentation that symptoms of obstructive sleep apnea are improved; *and*
- b. Objective evidence of adherence to use of the positive airway pressure device, reviewed by the treating physician. Adherence to therapy is defined as use of positive airway pressure four (4) or more hours per night on at least 70% of nights during a consecutive thirty (30) day period anytime during the initial period of usage.

II. Medically Necessary Accessories and Supplies

- A. The following accessories and supplies are considered medically necessary for members who meet criteria for positive airway pressure (PAP) devices:

1. Chinstrap

2. Disposable or non-disposable filters
3. Full face mask with positive airway pressure device**
4. Headgear
5. Heated or non-heated humidifier
6. Nasal interface (mask or cannula type) for positive airway pressure device
7. Oral interface for positive airway pressure device
8. Replacement cushions and pillows for nasal application device
9. Replacement interface for full face mask
10. Tubing for heated or non-heated humidifier.

** A nasal interface (mask or cannula type) may be used with a positive airway pressure device, with or without a head strap as an alternative to a full face mask. However, upgraded face mask is considered medically necessary only if there is documentation that the member needs a different mask because he/she cannot maintain CPAP pressures or that in order to get the pressure the mask needs to be so tight as to generate pressure sores.

B. The following positive airway pressure supplies are considered not medically necessary convenience items:

1. Positive airway pressure bed pillows
2. Batteries for positive airway pressure devices
3. DC adapters for positive airway pressure devices.

Note: Aetna follows Medicare DME MAC rules with respect to the usual medically necessary quantity of supplies for positive airway pressure devices.

Upon individual review, positive airway pressure devices are considered a medically necessary form of non-invasive ventilation for members with lung disease without OSA. See [CPB 0452 - Noninvasive Positive Pressure Ventilation \(./400_499/0452.html\)](#). Requests for these devices for non-invasive ventilation of members with lung disease are subject to medical review.

III. Oral Appliances

A. Mandibular advancement oral appliances to reduce upper airway collapsibility or tongue retaining devices are considered medically necessary for members who have sleep test results that meets *one* of the following criteria:

1. The AHI or RDI is greater than or equal to 15 events per hour with a minimum of 30 events; *or*
2. The AHI or RDI is greater than or equal to 5 and less than 15 events per hour with a minimum of 10 events and documentation of:
 - a. Documented history of stroke; *or*
 - b. Documented hypertension (systolic blood pressure greater than 140 mm Hg and/or diastolic blood pressure greater than 90 mm Hg); *or*
 - c. Documented ischemic heart disease; *or*
 - d. Documented symptoms of impaired cognition, mood disorders, or insomnia; *or*
 - e. Excessive daytime sleepiness (documented by either Epworth greater than 10 or MSLT less than 6); *or*
 - f. Greater than 20 episodes of oxygen desaturation (i.e., oxygen saturation of less than 85 %) during a full night sleep study, or any 1 episode of oxygen desaturation (i.e., oxygen saturation of less than 70 %); *or*
3. If the AHI is greater than 30 or the RDI is greater than 30 and meets *either* of the following:
 - a. The member is not able to tolerate a positive airway pressure (PAP) device; *or*
 - b. The use of a PAP device is contraindicated.

B. Replacement of oral appliances is considered medically necessary at the end of their 5-year RUL. Replacement of these items is considered medically necessary prior to the end of the 5-year RUL due to a change in the member's condition. Replacement needed due to misuse or abuse are not covered.

C. Oral appliances for snoring (e.g., Slow Wave DS8, and Snore Guard) are considered not medically necessary treatment of disease, as snoring is not considered a disease.

D. Compliance monitors for oral appliances have no proven value.

Note: The Oasys Oral Airway System, and the Silent Partner OSA appliance are considered equally effective to standard oral appliances. All follow-up care, including fitting, adjustments, modifications, professional services (not all-inclusive) required during the first 90 days after provision of the oral appliance are considered to be included in the payment for device.

Note: Dental rehabilitation services (dentures, bridgework, etc.) as treatment for OSA, even if medically necessary, are not available benefits under standard Aetna health insurance plans. Members should review their dental benefits plan, if any.

Note: The AM Aligner (an adjustable positioning dental device) is not covered because it is inclusive to the sleep appliance for the treatment of OSA

IV. Medically Necessary Surgeries and Procedures

Medically necessary procedures for the treatment of OSA in adults include:

A. *Adult Lingual or Pharyngeal Tonsillectomy and Adenoidectomy*

Aetna considers pharyngeal and lingual tonsillectomy medically necessary with UPPP or as an isolated procedure in adult OSA where hypertrophied tonsils compromise the airway space. An adenoidectomy is considered medically necessary for significant nasopharyngeal obstruction due to adenoid hyperplasia.

B. *Drug-Induced Sleep Endoscopy (DISE)*

Aetna considers the use of DISE medically necessary to evaluate appropriateness of FDA-approved hypoglossal nerve stimulation if multiple levels of obstruction are suspected, and when all of the criteria for hypoglossal nerve stimulation are met.

Aetna considers DISE experimental and investigational for all other indications because of insufficient evidence in the peer-reviewed published medical literature of its safety and effectiveness.

C. *Hypoglossal Nerve Neurostimulation*

Aetna considers Food and Drug Administration (FDA)-approved hypoglossal nerve neurostimulation (e.g., Inspire II System, Inspire 3028 system for Upper Airway Stimulation (UAS) Therapy) medically necessary for the treatment of moderate to severe obstructive sleep apnea when *all* of the following criteria are met:

1. Member is 18 years of age or older; *and*
2. Body mass index (BMI) is less than 40 kg/m²; *and*
3. A polysomnography (PSG) is performed within 24 months of first consultation for Inspire implant; *and*
4. Member has predominantly obstructive events (defined as central and mixed apneas less than 25% of the total AHI); *and*
5. Apnea hypopnea index (AHI) is 15 to 100 events per hour; *and*
6. Member has a minimum of one month of CPAP monitoring documentation that demonstrates CPAP failure (defined as AHI greater than 15 despite CPAP usage) or CPAP intolerance (defined as less than 4 hours per night, 5 nights per week); *and*
7. Absence of complete concentric collapse at the soft palate level as seen on a drug-induced sleep endoscopy (DISE) procedure; *and*
8. No other anatomical findings that would compromise performance of device (e.g., tonsil size 3 or 4 per tonsillar hypertrophy grading scale. See [Appendix](#)).

For hypoglossal nerve stimulation for adolescents with Down syndrome, see [CPB 0752 - Obstructive Sleep Apnea in Children \(./700_799/0752.html\)](#).

Aetna considers hypoglossal nerve neurostimulation experimental and investigational for all other indications.

Aetna considers non-FDA-approved hypoglossal nerve neurostimulation (e.g., the Apnex Hypoglossal Nerve Stimulation (HGNS™) System, the aura6000™ Neurostimulation System, ImThera's Targeted Hypoglossal Neurostimulation Therapy, and WellStar upper airway neurostimulation implant) experimental and investigational for the treatment of adult obstructive sleep apnea.

D. *Jaw Realignment Surgery* (i.e., hyoid myotomy and suspension, mandibular osteotomy, genioglossal advancement)

Aetna considers jaw realignment surgery medically necessary for persons who fail other treatment approaches for OSA.

Although jaw realignment surgery may be considered medically necessary on an individual case basis, because of the extent of surgery, these cases may be subject to review by Aetna's Oral and Maxillofacial Surgery Unit to assess medical necessity.

Note: According to the medical literature, persons undergoing jaw realignment surgery must usually also undergo orthodontic therapy to correct changes in occlusion associated with the surgery. Orthodontic therapy (i.e., the placement of orthodontic brackets and wires) is excluded from coverage under standard Aetna medical plans regardless of medical necessity. Please check benefit plan descriptions for details. Benefits for orthodontic therapy may be available under the member's dental plan, if any.

E. *Nasal Surgery*

Aetna considers nasal valve surgery, polypectomy, septoplasty, and turbinectomy medically necessary for adults with nasal obstruction and CPAP intolerance related to nasal issues and high pressure requirements. Aetna considers a turbinectomy medically necessary for severe nasal obstruction due to hypertrophied inferior nasal turbinates. Aetna considers a polypectomy medically necessary for

severe nasal obstruction due to nasal polyps. **Note:** Nasal valve surgery requires photos clearly documenting internal or external valve collapse contributing to nasal obstruction, per [CPB 0005 - Septoplasty and Rhinoplasty \(0005.html\)](#).

F. Palatopharyngoplasty

Palatopharyngoplasty (uvulopalatopharyngoplasty (UPPP), uvulopharyngoplasty, uvulopalatal flap, expansion pharyngoplasty, lateral pharyngoplasty, transpalatal advancement pharyngoplasty, relocation pharyngoplasty) is used to treat OSA by enlarging the oropharynx; it is considered medically necessary for OSA members who meet the criteria for CPAP or AutoPAP (see above), but who have had an inadequate response or are intolerant to CPAP or AutoPAP, despite adjustments to pressure and mask, as appropriate. (Intolerance includes claustrophobia, difficulty tolerating pressure, inability to sleep with CPAP device, intolerance of nasal or mouth interface, nasal irritation, or repeated removal of CPAP unintentionally during sleep.) The medical records must document that the member has attempted CPAP or AutoPAP before considering surgery.

Aetna considers palatopharyngoplasty experimental and investigational for persons with non-obstructive sleep apnea, upper airway resistance syndrome (UARS), and for all other indications.

G. The Zzoma Positional Device

Aetna considers the Zzoma positional device not medically necessary because it has not been proven to be superior to other interventions to keep a person in a non-supine position.

H. Tongue Base Reduction Surgery

Aetna considers tongue reduction procedures (midline glossectomy and lingualplasty) medically necessary for OSA to relieve obstruction in the lower pharyngeal airway.

I. Tonsillectomy

Aetna considers tonsillectomy medically necessary with UPPP in members who meet medical necessity criteria for UPPP (see above for criteria for CPAP or AutoPAP).

J. Tracheostomy

Aetna considers tracheostomy medically necessary for those members with the most severe OSA not manageable by other interventions. Requests for tracheostomy for OSA are subject to medical review. **Note:** Aetna follows Medicare DME MAC rules for the medically necessary quantity of tracheostomy supplies for OSA and other indications.

V. Experimental and Investigational

A. Diagnostic Procedures, Techniques, and Testing

The following diagnostic procedures, techniques, and testing are considered experimental and investigational in members with symptoms suggestive of OSA because their effectiveness for this indication has not been established:

1. Acoustic pharyngometry. See [CPB 0336 - Acoustic Pharyngometers and SNAP Testing System \(../300_399/0336.html\)](#); or
2. Actigraphy testing when used alone. Actigraphy, which consists of a small portable device that senses physical motion and stores the resulting information, has been used in research studies for the evaluation of rest-activity cycles. This technique, when used alone (single channel study), has not been validated as a method of diagnosing OSA. See [CPB 0710 - Actigraphy and Accelerometry \(../700_799/0710.html\)](#); or
3. Cephalographic X-rays for diagnosis of OSA. A single panoramic x-ray of the jaws and a lateral cephalometric x-ray are considered medically necessary for the evaluation for an oral appliance for OSA. A second lateral cephalometric x-ray

with the bite registration or oral appliance in place is considered medically necessary to visualize the mandibular repositioning and the changes in the airway space. Additional x-rays are considered medically necessary when surgical intervention for OSA is being considered; *or*

4. Daytime nap polysomnography; *or*
5. Diagnostic audio recording, with or without pulse oxymetry to diagnose sleep apnea; *or*
6. Dynamic sleep magnetic resonance imaging (MRI) for the diagnosis of OSA; *or*
7. Genetic association studies (e.g., tumor necrosis factor-alpha (TNFA) 308 A/G polymorphism, angiotensin-converting enzyme (ACE) gene insertion/deletion, apolipoprotein E (ApoE) polymorphism) for the diagnosis of obstructive sleep apnea; *or*
8. Laryngeal function studies; *or*
9. Maintenance of wakefulness test; *or*
10. Measurement of blood levels (serum and plasma) of C-reactive protein as a biomarker for the development of OSA; *or*
11. Measurement of blood levels (serum and plasma) of interleukin-8 as a biomarker for the development of OSA syndrome (OSAS); *or*
12. Measurement of blood levels (serum and plasma) of leptin as a biomarker for the development of OSAS; *or*
13. Measurement of central corneal thickness, intra-ocular pressure, and retinal nerve fiber layer thickness for grading severities of obstructive sleep apnea syndrome (OSAS); *or*
14. Measurement of circulating malondialdehyde concentrations as a biomarker for OSA; *or*
15. Measurement of Fas-positive lymphocytes for evaluation of systemic inflammation in OSAS; *or*
16. Measurement of plasma and serum interleukin-6 levels; *or*
17. Measurement of plasma and serum tumor necrosis factor-alpha; *or*
18. Measurement of serum/plasma brain-derived neurotrophic factor (BDNF) levels as a biomarker for OSA; *or*

19. Measurement of serum/plasma insulin-like growth factor 1 (IGF-1) levels for diagnosis of OSA hypopnea syndrome; *or*
20. Measurement of serum/plasma monocyte chemoattractant protein-1 (MCP-1) levels for diagnosis of OSA; *or*
21. Multiple sleep latency test (see [CPB 0330 - Multiple Sleep Latency Testing \(MSLT\)](#) and [Maintenance of Wakefulness Test \(MWT\)](#) ([./300_399/0330.html](#))); *or*
22. Natural sleep endoscopy for evaluation of OSA; *or*
23. Screening for asymptomatic OSA; *or*
24. SleepStrip; *or*
25. Sonography; *or*
26. The static charge sensitive bed; *or*
27. Tomographic X-ray; *or*
28. Upper gastro-intestinal endoscopy for diagnosing OSAS; *or*
29. Use of serum level of advanced glycation end-products as a biomarker of obstructive sleep apnea-hypopnea syndrome; *or*
30. Voxel-based brain morphometry (VBM) studies for evaluation of OSA; *or*
31. X-rays of the temporomandibular joint or sella turcica.

B. *Treatment*

The following are considered experimental and investigational for the treatment of obstructive sleep apnea (OSA) in adults because the effectiveness of these approaches has not been established:

1. A BiPAP device with a backup rate feature (e.g., adaptive servoventilation, VPAP Adapt SV) (see [CPB 0452 - Noninvasive Positive Pressure Ventilation](#) ([./400_499/0452.html](#)));
2. Daytime neuromuscular stimulation of the tongue (e.g., eXciteOSA);
3. Oral appliances for treatment of upper airway resistance syndrome (UARS);
4. Oral appliances to reduce upper airway collapsibility for indications other than OSA (see section III.A.); for policy on oral occlusal appliances used to treat temporomandibular joint (TMJ) disorders, see [CPB 0028 - Temporomandibular Disorders](#) ([0028.html](#));

5. Positive Airway pressure (PAP) for the treatment of persons with upper airway resistance syndrome (UARS) or for the improvement of seizure control in persons with epilepsy.

C. Surgeries and Procedures

The following surgeries and procedures are considered experimental and investigational for the treatment of OSA because its effectiveness has not been established:

1. Apnea-triggered muscle stimulation;
2. Cardiac (atrial) pacing;
3. Cautery-assisted palatal stiffening operation (CAPSO);
4. Contraction of the sternothyroid muscle with ansa cervicalis stimulation;
5. Devices for positional therapy (e.g., the Lunoa System);
6. Endoscopically-assisted surgical expansion (EASE);
7. Epiglottidectomy / partial epiglottidectomy;
8. Genioplasty and genial tubercle advancement;
9. Injection snoreplasty, injection of a sclerosing agent into the soft palate;
10. Mandibular distraction osteogenesis;
11. Nasal dilators;
12. Nasal expiratory positive airway pressure (EPAP) (e.g., the Provent Sleep Apnea Therapy, and the ULTepap System);
13. NighLase laser therapy for the treatment of snoring or OSA;
14. Pillar™ Palatal Implant System (Restore Medical, Inc.);
15. Rapid maxillary expansion;
16. Remotely controlled mandibular positioner as a predictive screening tool for oral appliances that protrude the mandible;
17. Respiratory muscle therapy (i.e., breathing exercises, oropharyngeal exercises, and wind musical instruments);
18. Somnoplasty and coblation (radiofrequency ablation of the tongue base, uvula or soft palate [Somnoplasty] or of the nasal passages and soft palate [Coblation] (see

[CPB 0592 - Radiofrequency Ablation of Hypertrophied Nasal Turbinates](#)

[\(../500_599/0592.html\)](#));

19. Surgical palatal expansion;
20. The Advance System (an adjustable tongue-advancement device);
21. The Repose (AIRvance Tongue Suspension) System and the Encore Tongue Base Suspension;

Aetna considers the AIRvance Tongue Suspension (formerly Repose) System, a minimally invasive technique involving tongue base suspension, and the Encore tongue base suspension, experimental and investigational. These procedures, also referred to as tongue stabilization, tongue stitch or tongue fixation, have been used for treating sleep disordered breathing (SDB) caused by tongue base collapse. No specific criteria exist regarding the diagnosis of tongue base collapse in SDB. Preliminary short-term studies of surgery targeted to alleviate tongue base collapse in SDB have shown subjective improvements in snoring and statistically significant decreases in mean RDI. However, the reported rates of success have been inconsistent among studies, and larger controlled studies with long-term follow-up are necessary to determine whether these lingual suspension procedures safe and effective.

22. The Winx Therapy System / oral pressure therapy;
23. Transcutaneous electrical nerve stimulation (TENS);
24. Uvulectomy and Laser Assisted Uvuloplasty (LAUP);

Cold knife uvulectomy and laser assisted uvuloplasty (LAUP, laser uvulectomy) are considered experimental and investigational for OSA because they have not been shown to be as effective as UPPP for this indication. However, Aetna may consider these procedures medically necessary, upon individual case review, for members with severe OSA who have other medical conditions that make them unable to undergo UPPP and have failed a trial of CPAP or AutoPAP or the use of an oral appliance or device. **Note:** Uvulectomy is considered medically necessary for uvular neoplasm and as an emergent treatment for acute edema of the uvula

causing acute respiratory distress. Uvulectomy is considered experimental and investigational as a treatment for recurrent throat infections and for all other indications.

VI. Related Policies

- [CPB 0005 - Septoplasty and Rhinoplasty \(0005.html\)](#)
- [CPB 0028 - Temporomandibular Disorders \(0028.html\)](#)
- [CPB 0330 - Multiple Sleep Latency Test \(MSLT\) and Maintenance of Wakefulness Test \(MWT\) \(../300_399/0330.html\)](#)
- [CPB 0336 - Acoustic Pharyngometers and SNAP Testing System \(../300_399/0336.html\)](#)
- [CPB 0452 - Noninvasive Positive Pressure Ventilation \(./400_499/0452.html\)](#)
- [CPB 0456 - Pillows and Cushions \(./400_499/0456.html\)](#)
- [CPB 0592 - Radiofrequency Ablation of Hypertrophied Nasal Turbinates \(./500_599/0592.html\)](#)
- [CPB 0710 - Actigraphy and Accelerometry \(./700_799/0710.html\)](#)
- [CPB 0752 - Obstructive Sleep Apnea in Children \(./700_799/0752.html\)](#)

CPT Codes / HCPCS Codes / ICD-10 Codes

Diagnosis:

Code	Code Description
CPT codes covered if selection criteria are met:	
70350	Cephalogram, orthodontic
70355	Orthopantogram
95800	Sleep study, unattended, simultaneous recording; heart rate, oxygen saturation, respiratory analysis (eg, by airflow or peripheral arterial tone) and sleep time

Code	Code Description
95801	minimum of heart rate, oxygen saturation, and respiratory analysis (eg, by airflow or peripheral arterial tone)
95806	Sleep study, simultaneous recording of ventilation, respiratory effort, ECG or heart rate, and oxygen saturation, unattended by a technologist
95807	Sleep study, simultaneous recording of ventilation, respiratory effort, ECG or heart rate, and oxygen saturation, attended by a technologist
95808	Polysomnography; any age, sleep staging with 1-3 additional parameters of sleep, attended by a technologist
95810	age 6 years or older, sleep staging with 4 or more additional parameters of sleep, attended by a technologist
95811	age 6 years or older, sleep staging with 4 or more additional parameters of sleep, with initiation of continuous positive airway pressure therapy or bilevel ventilation, attended by a technologist

CPT codes not covered for indications listed in the CPB:

Mandibular distraction osteogenesis, measurement of Fas-positive lymphocytes, use of serum level of advanced glycation end-products, Measurements of Plasma and Serum Interleukin-6 Levels, Measurements of Plasma and Serum Tumor Necrosis Factor Alpha Levels, dynamic sleep magnetic resonance imaging (MRI), measurement of blood levels (serum and plasma) of interleukin-8, measurement of blood levels (serum and plasma) of leptin, natural sleep endoscopy, circulating malondialdehyde concentrations, Serum/plasma brain-derived neurotrophic factor, Serum/plasma monocyte chemoattractant protein-1(MCP-1)- no specific code:

21120	Genioplasty; augmentation (autograft, allograft, prosthetic material
21121	Genioplasty; sliding osteotomy, single piece
21122	Genioplasty; sliding osteotomies, 2 or more osteotomies (eg, wedge excision or bone wedge reversal for asymmetrical chin)
21123	Genioplasty; sliding, augmentation with interpositional bone grafts (includes obtaining autografts)

Code	Code Description
21199	Osteotomy, mandible, segmental; with genioglossus advancement [genial tubercle advancement]
43200	Esophagoscopy, flexible, transoral; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
70100	Radiologic examination, mandible; partial, less than 4 views
70110	complete, minimum of 4 views
70240	Radiologic examination, sella turcica
70332	Temporomandibular joint arthrography, radiological supervision and interpretation
76101	Radiologic examination, complex motion (i.e., hypercycloidal) body section (e.g., mastoid polytomography), other than urography; unilateral
76102	bilateral
76514	Ophthalmic ultrasound, diagnostic; corneal pachymetry, unilateral or bilateral (determination of corneal thickness)
76536	Ultrasound, soft tissues of head and neck (e.g., thyroid, parathyroid, parotid), real time with image documentation
78300	Bone and/or joint imaging; limited area
82172	Apolipoprotein, each [apolipoprotein E (ApoE) polymorphism]
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [tumor necrosis factor-alpha (TNFA) 308 A/G polymorphism]
84305	Somatomedin
86140	C-reactive protein
86141	C-reactive protein; high sensitivity (hsCRP)
92100	Serial tonometry (separate procedure) with multiple measurements of intraocular pressure over an extended time period with interpretation and report, same day (eg, diurnal curve or medical treatment of acute elevation of intraocular pressure)

Code	Code Description
92134	Scanning computerized ophthalmic diagnostic imaging, posterior segment, with interpretation and report, unilateral or bilateral; retina
92520	Laryngeal function studies (i.e., aerodynamic testing and acoustic testing)
94760 - 94762	Noninvasive ear or pulse oximetry for oxygen saturation; single determination; multiple determinations (e.g., during exercise); or by continuous overnight monitoring (separate procedure) [as a screening method to rule out OSA]
95803	Actigraphy testing, recording, analysis, interpretation, and report (minimum of 72 hours to 14 consecutive days of recording)
95805	Multiple sleep latency or maintenance of wakefulness testing, recording, analysis and interpretation of physiological measurements of sleep during multiple trials to assess sleepiness

HCPCS codes covered if selection criteria are met:

A7049	Expiratory positive airway pressure intranasal resistance valve [ULTepap system]
D9954	Fabrication and delivery of oral appliance therapy (OAT) morning repositioning device
D9955	Oral appliance therapy (OAT) titration visit
D9956	Administration of home sleep apnea test
G0398	Home sleep study test (HST) with type II portable monitor, unattended; minimum of 7 channels: EEG, EOG, EMG, ECG/heart rate, airflow, respiratory effort and oxygen saturation
G0399	Home sleep test (HST) with type III portable monitor, unattended; minimum of 4 channels: 2 respiratory movement/airflow, 1 ECG/heart rate and 1 oxygen saturation
G0400	Home sleep test (HST) with type IV portable monitor, unattended; minimum of 3 channels

HCPCS codes not covered for indications listed in the CPB:

D0320	Temporomandibular joint arthrogram, including injection
D0321	Other temporomandibular joint films, by report
D0322	Tomographic survey

Code	Code Description
D0330	Panoramic film
D0340	Cephalometric film
D0701	Panoramic radiographic image – image capture only
D0702	2-D cephalometric radiographic image – image capture only
D9957	Screening for sleep related breathing disorders
E0445	Oximeter device for measuring blood oxygen levels non-invasively [as a screening method to rule out OSA]

ICD-10 codes covered if selection criteria are met:

G47.01 - G47.32, G47.34 - G47.9	Organic & non-organic sleep disorders
G47.33	Obstructive sleep apnea (adult) (pediatric)
I27.0	Primary pulmonary hypertension
R06.00 - R06.09	Dyspnea
R06.3	Periodic breathing
R06.83	Snoring
R06.89	Other abnormalities of breathing

ICD-10 codes not covered for indications listed in the CPB:

Z13.83	Encounter for screening for respiratory disorder NEC [asymptomatic OSA]
--------	---

Treatment:

Oral Appliances:

CPT codes not covered for indications listed in the CPB:

NightLaser Laser therapy –no specific code

HCPCS codes covered if selection criteria are met:

D9947	Custom sleep apnea appliance fabrication and placement
D9948	Adjustment of custom sleep apnea appliance
D9949	Repair of custom sleep apnea appliance

Code	Code Description
D9953	Reline custom sleep apnea appliance (indirect)
E0485	Oral device/appliance used to reduce upper airway collapsibility, adjustable or non-adjustable, prefabricated, includes fitting and adjustment [covered only for obstructive sleep apnea in persons that meet criteria for CPAP but who are intolerant to positive airway pressure devices]
E0486	Oral device/appliance used to reduce upper airway collapsibility, adjustable or non-adjustable, custom fabricated, includes fitting and adjustment [AM aligner inclusive sleep appliance]
S8262	Mandibular orthopedic repositioning device, each
ICD-10 codes covered if selection criteria are met:	
G47.33	Obstructive sleep apnea (adult) (pediatric)
ICD-10 codes not covered for indications listed in the CPB:	
F51.05	Insomnia due to other mental disorder
G47.00 - G47.09	Sleep disorders
G47.20 - G47.29	Circadian rhythm sleep disorder
G47.30	Sleep apnea, unspecified
G47.31	Primary central sleep apnea
G47.32	High altitude periodic breathing
G47.34	Idiopathic sleep related nonobstructive alveolar hypoventilation
G47.35	Congenital central alveolar hypoventilation syndrome
G47.36	Sleep related hypoventilation in conditions classified elsewhere
G47.37	Central sleep apnea in conditions classified elsewhere
G47.39	Other sleep apnea
G47.8 - G47.9	Other and unspecified sleep disturbances [disorders that remain a general symptom without a specifically identified sleep disorder diagnosis]
R06.81	Apnea, not elsewhere classified

Code	Code Description
<i>Continuous Positive Airway Pressure (CPAP) CPAP with pressure relief technology (eg, C-Flex, C-Flex +) autoPAP (APAP), and APAP with pressure relief technology (eg, A-Flex).</i>	
HCPCS codes covered if selection criteria are met:	
A4604	Tubing with integrated heating element for use with positive airway pressure device
A7027	Combination oral/nasal mask, used with continuous positive airway pressure device, each
A7028	Oral cushion for combination oral/nasal mask, replacement only, each
A7029	Nasal pillows for combination oral/nasal mask, replacement only, pair
A7030	Full face mask used with positive airway pressure device, each [replacement device is not covered due to misuse or abuse]
A7031	Face mask interface, replacement for full face mask, each [replacement device is not covered due to misuse or abuse]
A7032	Cushion for use on nasal mask interface, replacement only, each [replacement device is not covered due to misuse or abuse]
A7033	Pillow for use on nasal cannula type interface, replacement only, pair [replacement device is not covered due to misuse or abuse]
A7034	Nasal interface (mask or cannula type) used with positive airway pressure device, with or without head strap [replacement device is not covered due to misuse or abuse]
A7035	Headgear used with positive airway pressure device [replacement device is not covered due to misuse or abuse]
A7036	Chinstrap used with positive airway pressure device [replacement device is not covered due to misuse or abuse]
A7037	Tubing used with positive airway pressure device [replacement device is not covered due to misuse or abuse]
A7038	Filter, disposable, used with positive airway pressure device [replacement device is not covered due to misuse or abuse]

Code	Code Description
A7039	Filter, non-disposable, used with positive airway pressure device [replacement device is not covered due to misuse or abuse]
A7044	Oral interface used with positive airway pressure device, each
A7045	Exhalation port with or without swivel used with accessories for positive airway devices, replacement only
A7046	Water chamber for humidifier, used with positive airway pressure device, replacement, each
E0470	Respiratory assist device, bi-level pressure capability, without back-up rate feature, used with noninvasive interface, e.g., nasal or facial mask (intermittent assist device with continuous positive airway pressure device) [for OSA members intolerant of CPAP or AutoPAP, or for whom CPAP or AutoPAP is ineffective]
E0472	Respiratory assist device, bi-level pressure capability, with back-up rate feature, used with invasive interface, e.g., tracheostomy tube (intermittent assist device with continuous positive airway pressure device) [for OSA members intolerant of CPAP]
E0561	Humidifier, non-heated, used with positive airway pressure device [replacement device is not covered due to misuse or abuse]
E0562	Humidifier, heated, used with positive airway pressure device [replacement device is not covered due to misuse or abuse]
E0601	Continuous positive airway pressure (CPAP) device

HCPCS codes not covered for indications listed in the CPB:

A7049	Expiratory positive airway pressure intranasal resistance valve
E0471	Respiratory assist device, bi-level pressure capability, with back-up rate feature, used with noninvasive interface, e.g., nasal or facial mask (intermittent assist device with continuous positive airway pressure device)

ICD-10 codes covered if selection criteria are met [with AHI 15 or >]:

G47.33	Obstructive sleep apnea (adult) (pediatric)
--------	---

ICD-10 codes covered if selection criteria are met [with OSA and AHI 5-14]:

F06.30	Mood disorder due to known physiological condition, unspecified
--------	---

Code	Code Description
F34.81 - F39	Other and unspecified persistent mood (affective) disorders
G93.31, G93.32, G93.39	Postviral fatigue syndrome
I10 - I16.2	Hypertensive disease [documented systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mm Hg]
I21.09 - I25.9	Ischemic heart disease
I69.00 - I69.998	Sequelae of cerebrovascular disease [history of stroke]
R53.1 R53.81 - R53.83	Other malaise and fatigue [excessive daytime sleepiness by Epworth >10 or Multiple Sleep Latency Test (MSLT) <6]
Z86.73	Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits
Z86.79	Personal history of other diseases of circulatory system [history of stroke]

ICD-10 codes covered [for BIPAP, DPAP, VPAP, VPAP Adapt SV, and AutoPAP] if selection criteria are met [for OSA member intolerant of CPAP]:

G47.33	Obstructive sleep apnea (adult) (pediatric)
G47.34	Idiopathic sleep related nonobstructive alveolar hypoventilation [nocturnal hypoventilation]
G47.36	Sleep related hypoventilation/hypoxemia in conditions classified elsewhere [nocturnal hypoventilation]
G70.00 - G70.9	Myoneural disorders [restrictive thoracic disorders]
J40 - J44.9	Chronic lower respiratory diseases
M95.4	Acquired deformity of chest and rib [restrictive thoracic disorders]
Q67.8	Other congenital deformities of chest [restrictive thoracic disorders]

ICD-10 codes not covered for indications listed in the CPB:

G40.309 - G40.919	Generalized idiopathic epilepsy and epileptic syndromes [for the improvement of seizure control]
R56.9	Unspecified convulsions [for the improvement of seizure control]

Code	Code Description
<i>Nasal Dilators:</i>	No specific code
<i>Apnea-triggered Muscle Stimulation:</i>	No specific code
<i>SleepStrip:</i>	No specific code
<i>Encore Tongue Base Suspension:</i>	No specific code
<i>Winx Therapy System/Oral Pressure Therapy:</i>	No specific code
<i>Hypoglossal nerve neurostimulation :</i>	CPT codes covered if selection criteria are met:
31575	Laryngoscopy, flexible; diagnostic [evaluate appropriateness of FDA-approved hypoglossal nerve stimulation if multiple levels of obstruction are suspected, and when all of the criteria for hypoglossal nerve stimulation]
42975	Drug-induced sleep endoscopy, with dynamic evaluation of velum, pharynx, tongue base, and larynx for evaluation of sleep-disordered breathing, flexible, diagnostic [evaluate appropriateness of FDA-approved hypoglossal nerve stimulation if multiple levels of obstruction are suspected, and when all of the criteria for hypoglossal nerve stimulation]
64568	Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
64582	Open implantation of hypoglossal nerve neurostimulator array, pulse generator, and distal respiratory sensor electrode or electrode array
64583	Revision or replacement of chest wall respiratory sensor electrode or electrode array, including connection to existing pulse generator
64584	Removal of hypoglossal nerve neurostimulator array, pulse generator, and distal respiratory sensor electrode or electrode array

Code	Code Description
95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
95976	with simple cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
95977	with complex cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional

HCPCS codes covered if selection criteria are met:

C1767	Generator, neurostimulator (implantable), nonrechargeable
C1778	Lead, neurostimulator (implantable)
C1787	Patient programmer, neurostimulator
L8680	Implantable neurostimulator electrode, each
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

ICD-10 codes covered if selection criteria are met:

G47.33	Obstructive sleep apnea (adult) (pediatric)
--------	---

Uvulopalatopharyngoplasty (UPPP):

CPT codes covered if selection criteria are met:	
42145	Palatopharyngoplasty (e.g., uvulopalatopharyngoplasty, uvulopharyngoplasty) [for OSA members who meet criteria for CPAP but are intolerant]

ICD-10 codes covered if selection criteria are met [for OSA members who are intolerant of CPAP]:

G47.33	Obstructive sleep apnea (adult) (pediatric)
--------	---

Code	Code Description
ICD-10 codes not covered for indications listed in the CPB:	
F51.05	Insomnia due to other mental disorders
G47.00 - G47.09	Organic and non-organic sleep disorders
G47.20 - G47.29	Circadian rhythm sleep disorder
G47.30	Sleep apnea, unspecified
G47.31	Primary central sleep apnea
G47.32	High altitude periodic breathing
G47.34	Idiopathic sleep related nonobstructive alveolar hypoventilation
G47.35	Congenital central alveolar hypoventilation syndrome
G47.36	Sleep related hypoventilation in conditions classified elsewhere
G47.37	Central sleep apnea in conditions classified elsewhere
G47.39	Other sleep apnea
G47.8 - G47.9	Other and unspecified sleep disturbances
R06.81	Apnea, not elsewhere classified

Uvulectomy:

CPT codes covered if selection criteria are met:

42140	Uvulectomy, excision of uvula
-------	-------------------------------

ICD-10 codes covered if selection criteria are met:

C05.2	Malignant neoplasm of uvula
D00.04	Carcinoma in situ of soft palate [uvula]

Laser Assisted Uvuloplasty (LAUP):

CPT codes not covered for indications listed in the CPB:

42160	Destruction of lesion, palate or uvula (thermal, cryo or chemical)
42890	Limited pharyngectomy

HCPCS codes not covered for indications listed in the CPB:

S2080	Laser-assisted uvulopalatoplasty (LAUP)
-------	---

Code	Code Description
ICD-10 codes not covered for indications listed in the CPB:	
G47.00 - G47.09	Organic and non-organic sleep disorders
G47.8 - G47.9	Other and unspecified sleep disturbances
<i>Somnoplasty and Coblation:</i>	
CPT codes not covered for indications listed in the CPB:	
30801	Cautery and/or ablation, mucosa of inferior turbinates, unilateral or bilateral, any method; superficial [if used to report somnoplasty or coblation]
30802	intramural [if used to report somnoplasty or coblation]
41530	Submucosal ablation of the tongue base, radiofrequency, one or more sites, per session
ICD-10 codes not covered for indications listed in the CPB:	
G47.00 - G47.09	Organic and non-organic sleep disorders
G47.8 - G47.9	Other and unspecified sleep disturbances
R06.81	Apnea, not elsewhere classified
R06.89	Abnormalities of breathing
<i>The Repose System:</i>	
CPT codes not covered for indications listed in the CPB:	
41512	Tongue base suspension, permanent suture technique
<i>Adult Lingual or Pharyngeal Tonsillectomy and Adenoideectomy:</i>	
CPT codes covered if selection criteria are met:	
42821	Tonsillectomy and adenoideectomy age 12 or over [covered only for UPPP for adult OSA where the tonsils compromise the airway space]
42831	Adenoideectomy, primary age 12 or over
42836	Adenoideectomy, secondary; age 12 or over [pharyngeal]
42826	Tonsillectomy, primary or secondary; age 12 or over [covered only for UPPP for adult OSA where the tonsils compromise the airway space]

Code	Code Description
CPT codes not covered for indications listed in the CPB:	
42870	Excision or destruction lingual tonsil, any method (separate procedure) [as an isolated procedure]
ICD-10 codes covered if selection criteria are met:	
G47.33	Organic and non-organic sleep disorders (adult)
J35.1	Hypertrophy of tonsils
J35.2	Hypertrophy of adenoids [that results in significant nasopharyngeal obstruction]
J35.3	Hypertrophy of tonsils with hypertrophy of adenoids [that results in significant nasopharyngeal obstruction]
ICD-10 codes not covered for indications listed in the CPB:	
G47.00 - G47.09	Organic and non-organic sleep disorders (adult)
<i>Zzoma positional device:</i>	
HCPCS codes not covered for indications listed in the CPB:	
E0190	Positioning cushion/pillow/wedge, any shape or size, includes all components and accessories [Zzoma positional device]
<i>Jaw Realignment Surgery:</i>	
CPT codes covered if selection criteria are met:	
21198	Osteotomy, mandible, segmental [for OSA members who fail other treatment approaches]
21199	with genioglossus advancement [for OSA members who fail other treatment approaches]
21208	Osteoplasty, facial bones; augmentation (autograft, allograft, or prosthetic implant) [for OSA members who fail other treatment approaches]
21209	reduction [for OSA members who fail other treatment approaches]
21685	Hyoid myotomy and suspension [for OSA members who fail other treatment approaches]
ICD-10 codes covered if selection criteria are met:	
G47.33	Obstructive sleep apnea (adult) (pediatric)

Code	Code Description
<i>Tracheostomy:</i>	
CPT codes covered if selection criteria are met:	
31600 - 31601	Tracheostomy
ICD-10 codes covered if selection criteria are met:	
G47.33	Obstructive sleep apnea (adult) (pediatric) [for members with the most severe OSA not manageable by other interventions]
<i>Cardiac (Atrial) Pacing:</i>	
CPT codes not covered for indications listed in the CPB:	
33202 - 33249	Pacemaker procedures
ICD-10 codes not covered for indications listed in the CPB:	
G47.00 - G47.09	Organic and non-organic sleep disorders
G47.8 - G47.9	Other and unspecified sleep disturbances
R06.81	Apnea, not elsewhere classified
R06.89	Abnormalities of breathing
<i>Injection Snoreplasty:</i>	
No specific code	
<i>Cautery-Assisted Palatal Stiffening Operation (CAPSO):</i>	
CPT codes not covered for indications listed in the CPB:	
42950	Pharyngoplasty (plastic or reconstructive operation on pharynx) [if used to report CAPSO]
ICD-10 codes not covered for indications listed in the CPB:	
G47.00 - G47.09	Organic and non-organic sleep disorders
G47.8 - G47.9	Other and unspecified sleep disturbances
R06.81	Apnea, not elsewhere classified
R06.89	Abnormalities of breathing
<i>Pillar™ Palatal Implant System:</i>	
HCPCS codes not covered for indications listed in the CPB:	
C9727	Insertion of implants into the soft palate; minimum of three implants

Code	Code Description
ICD-10 codes not covered for indications listed in the CPB:	
G47.00 - G47.09	Organic and non-organic sleep disorders
G47.8 - G47.9	Other and unspecified sleep disturbances [if used to report OSA]
R06.81	Apnea, not elsewhere classified
R06.89	Abnormalities of breathing
<i>Transpalatal Advancement Pharyngoplasty:</i>	
CPT codes not covered for indications listed in the CPB:	
42145	Palatopharyngoplasty (e.g., uvulopalatopharyngoplasty, uvulopharyngoplasty) [if used to report transpalatal advancement pharyngoplasty]
42950	Pharyngoplasty (plastic or reconstructive operation on pharynx) [if used to report transpalatal advancement pharyngoplasty]
ICD-10 codes not covered for indications listed in the CPB:	
G47.00 - G47.09	Organic and non-organic sleep disorders
G47.8 - G47.9	Other and unspecified sleep disturbances [if used to report OSA]
R06.81	Apnea, not elsewhere classified
R06.89	Abnormalities of breathing
<i>Nasal Surgery:</i>	
CPT codes covered if selection criteria are met:	
30110 - 30115	Excision, nasal polyp(s)
30130	Excision inferior turbinate, partial or complete, any method
30140	Submucous resection inferior turbinate, partial or complete, any method
31237 - 31240	Nasal/sinus endoscopy
CPT codes not covered for indications listed in the CPB:	
30000 - 30100, 30117 - 30125 30150 - 31235, 31254 - 30999	Surgery/Respiratory System, nose/nasal

Code	Code Description
HCPCS codes not covered for indications listed in the CPB:	
C9749	Repair of nasal vestibular lateral wall stenosis with implant(s)
ICD-10 codes covered if selection criteria are met:	
J33.0 - J33.9	Nasal polyp
J34.3	Hypertrophy of nasal turbinates
R09.81	Nasal congestion [Nasal obstruction]
ICD-10 codes not covered for indications listed in the CPB:	
G47.00 - G47.09	Organic and non-organic sleep disorders
G47.33	Obstructive sleep apnea (adult) (pediatric)
G47.8 - G47.9	Other and unspecified sleep disturbances [if used to report OSA]
R06.81	Apnea, not elsewhere classified
R06.89	Abnormalities of breathing
<i>Glossectomy:</i>	
CPT codes covered for indications listed in the CPB:	
41120	Glossectomy; less than one-half tongue
41130	Hemiglossectomy
ICD-10 codes covered for indications listed in the CPB:	
G47.33	Obstructive sleep apnea (adult) (pediatric)
<i>Expansion sphincteroplasty, Provent sleep apnea therapy, WellStar upper airway neurostimulation implant:</i>	
No specific code	
<i>Epiglottidectomy/partial epiglottidectomy:</i>	
CPT codes not covered for indications listed in the CPB:	
31420	Epiglottidectomy
ICD-10 codes not covered for indications listed in the CPB:	
G47.33	Obstructive sleep apnea (adult) (pediatric)

Code	Code Description
<i>Positional therapy:</i>	
HCPCS codes not covered for indications listed in the CPB:	
E0530	Electronic positional obstructive sleep apnea treatment, with sensor, includes all components and accessories, any type
ICD-10 codes not covered for indications listed in the CPB:	
G47.33	Obstructive sleep apnea (adult) (pediatric) [positional]
<i>Respiratory muscle therapy:</i>	
HCPCS codes not covered for indications listed in the CPB:	
G0237	Therapeutic procedure to increase strength or endurance of respiratory muscles, face to face, one on one, 15 minutes each (including monitoring)
G0238	Therapeutic procedures to improve respiratory function, other than described by G0237, one-on-one, face-to-face, per 15 minutes (includes monitoring)
G0239	Therapeutic procedures to improve respiratory function or increase strength or endurance of respiratory muscles, two or more individuals (includes monitoring)
ICD-10 codes not covered for indications listed in the CPB:	
G47.33	Obstructive sleep apnea (adult) (pediatric)
<i>Surgical Palatal Expansion:</i>	
CPT codes not covered for indications listed in the CPB:	
<i>Surgical Palatal Expansion: No specific code</i>	
ICD-10 codes not covered for indications listed in the CPB:	
G47.33	Obstructive sleep apnea (adult) (pediatric)
<i>Endoscopically-Assisted Surgical Expansion (EASE):</i>	
CPT not covered for indications listed in the CPB:	
<i>Endoscopically-Assisted Surgical Expansion (EASE): No specific code</i>	
ICD-10 codes not covered for indications listed in the CPB:	
G47.33	Obstructive sleep apnea (adult) (pediatric)

Code	Code Description
<i>Transcutaneous Electrical Nerve Stimulation (TENS):</i>	
HCPCS codes not covered for indications listed in the CPB:	
E0720	Transcutaneous electrical nerve stimulation (tens) device, two lead, localized stimulation
E0730	Transcutaneous electrical nerve stimulation (tens) device, four or more leads, for multiple nerve stimulation
ICD-10 codes not covered for indications listed in the CPB:	
G47.33	Obstructive sleep apnea (adult) (pediatric)
<i>Slow Wave DS8 (an intra-oral device):</i>	
HCPCS codes not covered for indications listed in the CPB:	
K1027	Oral device/appliance used to reduce upper airway collapsibility, without fixed mechanical hinge, custom fabricated, includes fitting and adjustment
ICD-10 codes not covered for indications listed in the CPB:	
R06.83	Snoring
<i>Contraction of the Sternothyroid Muscle with Ansa Cervicalis Stimulation:</i>	
CPT codes not covered for indications listed in the CPB:	
<i>Contraction of the Sternothyroid Muscle with Ansa Cervicalis Stimulation -no specific code</i>	
ICD-10 codes not covered for indications listed in the CPB:	
G47.33	Obstructive sleep apnea (adult) (pediatric)
<i>Daytime Neuromuscular Stimulation of the Tongue:</i>	
HCPCS codes not covered for indications listed in the CPB:	
E0490	Power source and control electronics unit for oral device/appliance for neuromuscular electrical stimulation of the tongue muscle, controlled by hardware remote
E0491	Oral device/appliance for neuromuscular electrical stimulation of the tongue muscle, used in conjunction with the power source and control electronics unit, controlled by hardware remote, 90-day supply
E0492	Power source and control electronics unit for oral device/appliance for neuromuscular electrical stimulation of the tongue muscle, controlled by phone application

Code	Code Description
E0493	Oral device/appliance for neuromuscular electrical stimulation of the tongue muscle, used in conjunction with the power source and control electronics unit, controlled by phone application, 90-day supply
ICD-10 codes not covered for indications listed in the CPB:	
G47.33	Obstructive sleep apnea (adult)(pediatric)

Background

Airway obstruction during sleep is a commonly recognized problem, which may be associated with significant morbidity. Various diagnostic studies and treatment approaches are employed in managing this condition.

Data from the history and physical examination have been shown to be sensitive but not specific for diagnosing obstructive sleep apnea (OSA). According to available guidelines (ICSI, 2006), the following signs and symptoms may suggest significant risk for OSA: reported apneas by sleep partner; awakening with choking; intense snoring; severe daytime sleepiness, especially with impairment of driving; male gender and post-menopausal females; obesity (body mass index [BMI] greater than or equal to 30); large neck circumference; and hypertension.

An increased risk of moderate to severe OSA is indicated by the presence of excessive daytime sleepiness and at least two of the following three criteria: habitual loud snoring, witnessed apnea or gasping or choking, or diagnosed hypertension (Kapur, et al., 2017). Patients who do not meet these criteria in whom there is a concern for OSA based on a comprehensive sleep evaluation should be evaluated with polysomnography.

Polysomnography, or home sleep apnea testing with a technically adequate device, should be used for the diagnosis of OSA in uncomplicated adult patients presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA. Diagnostic testing for OSA should be performed in conjunction with a comprehensive sleep evaluation and adequate follow-up.

Diagnostic tests for OSA can be classified into 4 types. The most comprehensive type is Type I: attended, or in-facility polysomnography (PSG). There are 3 categories of portable monitors (used in both attended and unattended settings). Type II monitors have a minimum of 7 channels (e.g., electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), heart rate, airflow, respiratory effort, oxygen saturation). Type III monitors have a minimum of 4 monitored channels including ventilation or airflow (at least 2 channels of respiratory movement or respiratory movement and airflow), heart rate or ECG, and oxygen saturation. Type IV are all other monitors that fail to fulfill criteria for type III monitors. These are split into 2 subgroups: those assessing 3 or more bioparameters (i.e., most newer monitors fall here) and those assessing 1 or 2 bioparameters (i.e., the original ASDA level IV category) (see [Appendix](#)).

Examples of type II, III and IV monitors include: AccuSom, Alice PDx Portable Sleep System, ApneaLink Plus, ApneaLink Air, ARES, SleepView, Stardust II, and Watch-PAT.

Polysomnography (NPSG) is the standard diagnostic test for the diagnosis of OSA in adult patients in whom there is a concern for OSA based on a comprehensive sleep evaluation. NPSG performed in a sleep laboratory (Type I) is a definitive diagnostic tool to confirm the presence and severity of upper airway obstruction. According to current guidelines, a minimum 6-hour NPSG is preferred, which allows for the assessment of variability related to sleep stage and position with respect to the frequency of obstructive respiratory events and the occurrence of other types of nocturnal events such as periodic limb movements.

According to the available literature, NPSG performed in a sleep laboratory should include EEG, EOG, EMG, oronasal airflow, chest wall effort, body position, snore microphone, ECG, and oxyhemoglobin saturation. However, diagnostic NPSG may be performed in a healthcare facility,

or for appropriate cases, in the patient's home. The use of unattended home sleep monitoring using a Type II, III, or IV device, may identify apnea-hypopnea index (AHI) suggestive of obstructive sleep apnea-hypopnea syndrome (OSAHS). A technology assessment by the Agency for Healthcare Research and Quality (AHRQ) on *Home Diagnosis of Obstructive Sleep Apnea-Hypopnea Syndrome* (2007) commissioned by the Centers for Medicare & Medicaid Services (CMS), reported the following: Type II monitors identify AHI suggestive of obstructive sleep apnea-hypopnea syndrome (OSAHA) with high positive ratios (greater than 10) and low negative likelihood ratios (less than 0.1) both when the portable monitors were studied in the sleep laboratory and at home. Type III monitors may have the ability to predict AHI suggestive of OSAHA with high positive likelihood ratios and low negative likelihood ratios for various AHI cut-offs in laboratory-based PSG, especially when manual scoring is used. The ability of type III monitors to predict AHI suggestive of OSAHS appears to be better in studies conducted in sleep laboratories compared to studies in the home setting. Some studies of type IV devices also showed high positive likelihood ratios and low negative likelihood ratios, at least for selected sensitivity and specificity pairs from ROC curve analyses. Similarly to type III devices, the ability of type IV devices to predict AHI suggestive of OSAHS appears to be better in studies conducted in sleep laboratories.

A Decision Memorandum from the Centers for Medicare & Medicaid Services (CMS, 2009) concluded that there is sufficient evidence to support the use of devices that measure 3 or more channels that include actigraphy, oximetry, and peripheral arterial tone (e.g., Watch-PAT 100, Itamar Medical, Inc.) to aid the diagnosis of OSA in persons who have signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility. An assessment by the California Technology Assessment Forum (Tice, 2009) found sufficient evidence to support the use of the Watch-PAT device for diagnosis of OSA.

Clinical guidelines on the use of unattended home (portable) monitoring devices for the diagnosis of obstructive sleep apnea in adults, from the American Academy of Sleep Medicine (Collop, et al., 2007) for the diagnosis of OSA should be performed only in conjunction with a comprehensive sleep evaluation. The guidelines state that unattended sleep studies are not appropriate for the diagnosis of OSA in patients with significant comorbid medical conditions that may degrade the accuracy of unattended sleep studies, including moderate to severe pulmonary disease,

neuromuscular disease, or congestive heart failure. The guidelines note that unattended sleep studies are not appropriate for the diagnostic evaluation of OSA in patients suspected of having other sleep disorders. The guidelines state that unattended sleep studies are not appropriate for general screening of asymptomatic populations.

According to the American Academy of Sleep Medicine (AASM) guidelines (Collop et al, 2007), unattended sleep studies may be indicated for the diagnosis of OSA in patients for whom in-laboratory NPSG is not possible by virtue of immobility, safety, or critical illness. Unattended sleep studies may be indicated to monitor the response to non-continuous positive airway pressure (CPAP) treatments for obstructive sleep apnea, including oral appliances, upper airway surgery, and weight loss. The guidelines note that in laboratory NPSG may be indicated in cases where unattended sleep studies are technically inadequate or fail to establish the diagnosis of OSA in patients with a high pretest probability.

Updated guidelines from the American Academy of Sleep Medicine (Kapur, et al., 2017) state that attended NPSG should be used for diagnosis in patients in whom there is a concern for significant non-respiratory sleep disorder(s) that require evaluation (e.g., disorders of central hypersomnolence, parasomnias, sleep related movement disorders) or interfere with accuracy of unattended (home) sleep studies (e.g., severe insomnia); or environmental or personal factors that preclude the adequate acquisition and interpretation of data from unattended sleep studies. The guidelines state that attended NPSG, rather than home sleep apnea testing, be used for the diagnosis of OSA in patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to neuromuscular condition, awake hypoventilation or suspicion of sleep related hypoventilation, chronic opioid medication use, history of stroke or severe insomnia. NPSG is required for the diagnosis of non-obstructive sleep-disordered breathing (e.g., central sleep apnea, hypoventilation and sleep related hypoxemia).

The guidelines state that a technically adequate home sleep study device incorporates a minimum of the following sensors: nasal pressure, chest and abdominal respiratory inductance plethysmography, and oximetry; or else PAT with oximetry and actigraphy (Kapur, et al., 2017). A

home sleep study protocol that includes a single night recording is adequate for the diagnosis of OSA. If a single home sleep apnea test is negative, inconclusive, or technically inadequate, attended NPSG should be performed for the diagnosis of OSA.

According to the American Sleep Disorders Association (ASDA) (1997), split-night study NPSG is indicated for patients with an AHI greater than 40 events/hour during the first 2 hours of a diagnostic NPSG. Split-night studies may also be considered for patients with an AHI of 20 to 40 events/hour, based on clinical observations, such as the occurrence of obstructive respiratory events with a prolonged duration or in association with severe oxygen desaturation. Split-night studies require the recording and analysis of the same parameters as a standard diagnostic NPSG. Accepted guidelines provide that the diagnostic portion of a split-night study should be at least 2 hours duration. A minimum of 3 hours sleep is preferred to adequately titrate CPAP after this treatment is initiated.

Following a standard diagnostic NPSG, the available literature indicates that OSA patients should receive CPAP titration to specify the lowest CPAP level, which abolishes obstructive apneas, hypopneas, respiratory-effort related arousals, and snoring in all sleep positions and sleep stages. On occasion, an additional full-night CPAP titration NPSG may also be required following split-night study if the split-night NPSG did not allow for the abolishment of the vast majority of obstructive respiratory events or prescribed CPAP treatment does not control clinical symptoms. Alternatively, persons diagnosed with portable monitoring may be prescribed an auto-titrating positive airway pressure device (AutoPAP) that does not require attended titration.

According to guidelines from the American Academy of Sleep Medicine (Chesson et al, 1997), polysomnography with video recording and additional EEG channels in an extended bilateral montage may be indicated to assist with the diagnosis of paroxysmal arousals or other sleep disruptions that are thought to be seizure related when the initial clinical evaluation and results of a standard EEG are inconclusive.

Accepted guidelines indicate that nocturnal pulse oximetry alone is not appropriately used as a case finding or screening method to rule out OSA. Pulse oximetry, when used alone, has not been shown to have an adequate negative predictive value to rule out OSA (i.e., all patients with

symptoms suggestive of OSA would require polysomnography regardless of whether the pulse oximetry was positive or negative).

The MESAM and the static charge sensitive bed have not been proven to be valid devices for screening or diagnosing OSA. Actigraphy has not been validated as a method of screening or diagnosing OSA although it may be a useful adjunct to other procedures in the evaluation of sleep disorders.

Although the cephalometric x-ray is not necessary for the diagnosis of OSA, it is necessary for certain non-surgical and surgical treatments. A lateral cephalometric x-ray is very helpful if an anterior mandibular osteotomy is being performed for genioglossus advancement, or if maxillomandibular surgery is being planned for surgical correction of OSA. It is also helpful in analyzing hyoid position, posterior airway space, and other cephalometric parameters used in the treatment of OSA. For sleep apnea appliances for OSA, a pre-treatment lateral cephalometric x-ray and a second cephalometric X-ray with the bite registration or appliance in place may be necessary to visualize the mandibular repositioning and the changes in the airway space.

Uvulopalatopharyngoplasty (UPPP), jaw realignment surgery, positive airway pressure devices (e.g., CPAP, BiPAP, etc.), tracheostomy, tonsillectomy and adenoidectomy, and orthodontic devices such as the tongue retaining device, may be effective treatments for properly selected patients with OSA.

Several small scale studies have examined adult tonsillectomy as treatment for tonsil hypertrophy. Martinho et al (2006) evaluated seven moderately obese obstructive sleep apnea-hypopnea syndrome (OSAHS) with obstructive palatine tonsil hypertrophy patients who were treated with tonsillectomy. The authors reported that tonsillectomy resulted in a significant reduction in AHI post-operatively and concluded that tonsillectomy could be considered an option for obese OSAHS patients with significant tonsil hypertrophy when CPAP is not possible as the first choice of treatment.

Verse et al (2000) evaluated 11 patients with substantial tonsilar hypertrophy who had undergone tonsillectomy as single-treatment. The patient population included 5 patients with severe OSA, 4 with mild OSA, and 2 patients who were simple snorers with an AHI below 10. The results of 3 to 6 months of follow-up showed surgical response rates were 80 % in severe apneics and 100 % in mild apneics. However, Verse et al also noted that substantial tonsilar hypertrophy can rarely cause OSA in adults and that their patient population was carefully selected to determine if tonsillectomy was an effective and safe surgical option in treating this disorder.

With respect to simple tonsillectomy as a treatment for adult OSA, updates to the American Academy of Sleep Medicine practice parameters for the treatment of OSA state that classic upper airway surgical techniques such as nasal-septal reconstruction, cauterization, and tonsillectomy frequently fail to correct OSA (Aurora et al, 2010).

The Food and Drug Administration (FDA) has cleared numerous types of CPAP devices under the 510(k) process. These include but are not limited to many devices that allow a patient to wear a device that collects airflow and other patient measurements into a device that records data, while treating OSA with that device. The patient then takes the device to the physician and the physician downloads information that determines whether the patient has apnea sleep-related breathing disorder including OSA or needs further sleep studies or assessment. There are currently many sleep assessment devices on the market cleared by the FDA through the 510(k) process for use in the home. Patients may have a 3-month trial period of CPAP to assess appropriate therapeutic use and response. Reports obtained via a compliance monitor may be included when making this determination.

A variety of oral appliances and prostheses, including tongue retainers and mandibular advancing devices, have been used to treat patients with OSA. These devices modify the airway by changing the posture of the mandible and tongue. A task force of the Standards of Practice Committee of the ASDA concluded that, despite the considerable variation in the design of these devices, their clinical effects in improving OSA have been consistent (Kushida et al, 2006). These devices have been shown to be effective in alleviating OSA, and present a useful alternative to CPAP or surgery (Ferguson et al, 2006; Gotsopoulos et al, 2002). Oral appliances, however, have been shown to be less reliable and effective than CPAP, and therefore the literature

suggests that their use should generally be reserved for patients who are intolerant of CPAP. Oral appliances can be pre-fabricated or custom-fabricated. There is evidence of the efficacy of both pre-fabricated and custom-fabricated appliances for OSA (Vanderveken et al, 2008; Henke et al, 2000).

Patients with OSA suffer from numerous apneic events while sleeping, due to collapse of the upper airway during inspiration. Continuous positive airway pressure, and more recently, BiPAP, DPAP, VPAP, and AutoPAP, have been used in the treatment of OSA as a means of serving as a "pneumatic splint" in order to prop open the airways during inspiration.

Bilevel positive airway pressure, DPAP, and VPAP have been shown to be effective alternatives to CPAP, but are indicated only as second line measures for patients who are intolerant to CPAP. These alternatives to CPAP may also be indicated for OSA patients with concomitant breathing disorders to include restrictive thoracic disorders, COPD, and nocturnal hypoventilation. Long-term adherence to CPAP therapy was initially reported to range from 65 to 80 % (Nino-Murcia et al, 1989; Waldhorn et al, 1990; Rolfe et al, 1991; Hoffstein et al, 1992) with 8 to 15 % of patients refusing to accept treatment (Waldhorn, 1990; Krieger, 1992) after a single night's use. Other studies have evaluated compliance as regular CPAP use. More recent studies have shown up to 80 % of patients falling into the category of regular users (Pepin et al, 1999).

OPAP (Oral Pressure Appliance) is a custom fabricated intra-oral device that is used with a positive airway pressure device (e.g., CPAP, BiPAP, etc.) in place of a standard nasal mask. The oral pressure appliance positions the lower jaw forward to maximize the forward movement of the tongue and soft tissues of the back of the throat. In addition, the device has a chamber that, according to the manufacturer, allows air flow and pressure to be delivered into the back of the throat and thereby "splint" the soft tissues of the upper airway and prevent their collapse during sleep. The oral pressure appliance is custom fitted by a dentist specializing in dental appliances for sleep disorders. The OPAP method of treatment is similar to nasal mask delivery of air pressure with CPAP or BiPAP. The oral pressure appliance is connected to the end of the hose coming from the CPAP or BiPAP, and the pressure is adjusted in the same way as through the nose. OPAP differs from nasal masks in that it does not require head gear to hold it in place. It is inserted into the mouth and held in place by the upper and lower teeth. At present, no studies of

OPAP have been published in peer-reviewed medical journals. Therefore, one is unable to draw any conclusions about the effectiveness of OPAP compared to a standard nasal mask in treatment of patients with obstructive sleep apnea.

Pressure relief technology (eg, A-Flex, Bi-Flex, C-Flex, and C-Flex +) has been developed for PAP devices and provides pressure relief at critical points in the breathing cycle. This technology has become widely used in PAP devices and is purported to increase comfort and compliance with therapy.

In contrast to fixed CPAP, flexible positive airway pressure (C-Flex, Resironics, Murraysville, PA) (also known as pressure-relief CPAP) is characterized by a pressure reduction at the beginning of expiration. Flexible positive airway pressure is intended to improve patient satisfaction and compliance over standard CPAP. To compare adherence and clinical outcomes between flexible positive airway pressure CPAP, Aloia et al (2005) conducted a nonrandomized, open-label controlled trial of CPAP therapy versus therapy using the C-Flex device in persons with moderate-to-severe OSA. Study participants received either therapy with CPAP ($n = 41$) or with the C-Flex device ($n = 48$), depending on the available treatment at the time of recruitment, with those recruited earlier receiving CPAP therapy and those recruited later receiving therapy with the C-Flex device. The mean (+/- SD) treatment adherence over the 3-month follow-up period was higher in the C-Flex group compared to the CPAP group (weeks 2 to 4, $4.2 +/ - 2.4$ versus $3.5 +/ - 2.8$, respectively; weeks 9 to 12, $4.8 +/ - 2.4$ versus $3.1 +/ - 2.8$, respectively). The investigators reported that change in subjective sleepiness and functional outcomes associated with sleep did not improve more in one group over the other. Self-efficacy showed a trend toward being higher at the follow-up in those patients who had been treated with the C-Flex device compared to CPAP treatment. The investigators concluded that therapy with the C-Flex device may improve overall adherence over 3 months compared to standard therapy with CPAP. The investigators stated that clinical outcomes do not improve consistently, but C-Flex users may be more confident about their ability to adhere to treatment. The investigators concluded that randomized clinical trials are needed to replicate these findings.

A study by Nilius et al (2006) found no significant differences between C-Flex and CPAP in effectiveness and compliance. During the first night of treatment, patients receiving C-Flex had less dryness of the mouth, but this difference disappeared over a period of 7 weeks. The investigators conducted a study to compare polysomnographic data and compliance in sleep apnea patients receiving continuous positive airway pressure (CPAP) and C-Flex. A total of 52 persons newly diagnosed with OSA underwent conventional CPAP titration. Thereafter, polysomnography was performed at the titrated pressure using both the fixed CPAP pressure mode and the C-Flex mode in a randomized crossover approach. The patients were then discharged home for 7 weeks of treatment with the last-applied treatment mode, and compliance data were established at the end of that time. The average AHI was 5.8/hour with CPAP, and 7.0/hour with C-Flex. The investigators reported that compliance after 7 weeks was, on average, 9.4 mins longer with C-Flex than with CPAP, a difference that was not statistically significant.

Evaluation of a 13-item questionnaire (the fewer the complaints, the lower the score) showed no significant difference between scores for C-Flex (16.4) and CPAP (18.1). With regard to oral dryness, the score with C-Flex (1.4) was significantly lower than with CPAP (1.9) ($p < 0.05$). The investigators reported that this difference in oral dryness score was no longer detectable after 7 weeks. The investigators concluded that further studies are needed.

According to the Standard of Practice Committee of the American Academy of Sleep Medicine (Littner et al, 2002), central apnea may occur in some OSA patients with congestive heart failure (CHF) during CPAP titration after the airway obstruction of OSA is treated. Other patients with OSA may have central apneas after arousals as they fall back to sleep or which are the result of excessive CPAP pressure. Attempts to identify central apnea by detecting cardiac oscillations in the airflow tracing during polysomnography are not reliable because the airway can close during central apnea and the oscillations may not appear.

Adaptive servo-ventilation (ASV), a novel method of ventilatory support, is considered a bilevel positive airway pressure with a backup rate feature, and uses an automatic, minute ventilation-targeted device (VPAP Adapt, ResMed, Poway, CA) that performs breath to breath analysis and adjusts its settings accordingly. Depending on breathing effort, the device will automatically adjust the amount of airflow it delivers in order to maintain a steady minute ventilation. Most studies on the use of ASV have investigated its use for heart failure patients with central apnea or Cheyne-

Stokes respiration (Teschler et al, 2001; Pepperell et al, 2003; Töpfer et al, 2004; Pepin et al, 2006; Kasai et al, 2006; Zhang et al, 2006; Banno et al, 2006; Morrell et al, 2007; Morgenthaler et al, 2007; Hastings et al, 2010). Consistent with Durable Medical Equipment Medicare Administrative Carrier (DME MAC) policy, bilevel positive airway pressure with a backup rate feature is considered experimental and investigational for OSA (NHIC, 2008).

While virtually all studies report that surgical treatment of OSA improves snoring and daytime sleepiness, improvements in objective outcomes have been inconsistent with successful results of UPPP ranging from 50 % to 75 %. Fujita is credited with developing the UPPP as a method of enlarging the oropharynx (Fujita et al, 1985). He based the UPPP on his observation that patients with OSA, without other obvious sites of obstruction, often have a large edematous uvula, wide posterior tonsillar pillar mucosa and redundant mucosal folds in the lateral posterior pharyngeal walls extending from the nasopharynx to the hypopharynx. The surgery attempts to remove the redundant tissue but preserve the underlying muscular layer. In brief, the mucosae and submucosae of the soft palate, tonsillar fossa and the lateral aspect of the uvula are resected. The posterior pillar may be resected if contributing to the narrowing. In essence the amount of tissue removed is individualized for each patient, determined by the potential space and the width of the tonsillar pillar mucosa between the 2 palatal arches (Fujita et al, 1985). For a detailed discussion of the UPPP technique and its variants see the review by Koopmann and Moran (1990).

The UPPP enlarges the oropharynx but cannot correct obstructions in the hypopharynx. Early on it was recognized that UPPP failed in about 50 % of unselected patients with OSA. Riley et al (1990) and Crumley et al (1987) proposed that these failures may have been caused by an obstruction at the base of the tongue. The surgical approach to this problem has been to either modify the tongue itself or reposition the tongue by repositioning the mandible and/or maxilla.

Riley and Guilleminault and colleagues at the Sleep Disorders Center at Stanford University (Palo Alto CA) have been the primary early advocates of maxillofacial surgery for those patients who fail other treatment approaches. A stepwise protocol has been described (Riley et al, 1986; Riley et al, 1989; Riley et al, 1990). For example a hyoid resuspension can be done at the time of a UPPP. In this procedure the hyoid is resuspended anteriorly and superiorly from the

mandible with strips of fascia lata harvested from the thigh. In this way the tongue is moved anteriorally. If the patient fails this treatment, he/she then becomes eligible for the maxillary and mandibular osteotomy (MMO). While the purpose of this procedure is to enlarge the hypopharynx by advancing the mandible, the maxilla is also advanced to permit greater advancement of the mandible and to provide optimal esthetics. The maxilla is advanced by a Le Fort I osteotomy with rigid fixation and the mandible by a bilateral sagittal ramus split. The fixation must be maintained for one to three weeks. If a dental malocclusion is created by this surgery, the MMO must be preceded by a total mandibular subapical osteotomy with retropositioning of the dentition and bilateral repositioning of the inferior alveolar nerve. All 3 of the above procedures are frequently preformed in conjunction with removal of fatty tissue of the neck.

Jaw realignment is an aggressive, multi-step procedure requiring a 3- to 6-month interval between each step. According to the medical literature, jaw realignment surgery is generally reserved for those patients who fail other treatment approaches for OSA. An NIH Statement (1995) and American Sleep Disorders Association Guidelines (1996) state that jaw realignment surgery is a promising treatment for OSA. A systematic review of the evidence prepared for the American Sleep Disorders Association by Scher et al (1996), concluded that inferior sagittal mandibular osteotomy and genioglossal advancement with or without hyoid myotomy and suspension appears to be the most promising of procedures directed at enlarging the retrolingual region. The ASDA assessment stated that most of the experience with genioglossal advancement with or without hyoid suspension has been in conjunction with or following UPPP. Jaw fixation is necessary for 2 to 3 weeks following surgery, and a soft diet is necessary for a total of 6 weeks. Patients undergoing jaw realignment surgery must usually also undergo orthodontic therapy to correct changes in occlusion associated with the surgery. Jaw realignment surgery is generally reserved for those patients who fail other treatment approaches for OSA. According to the medical literature, patients undergoing jaw realignment surgery must usually also undergo orthodontic therapy to correct changes in occlusion associated with the surgery.

Tracheostomy, which simply bypasses the obstructing lesion of the upper airways, has been shown to be the most effective and predictable surgical approach to OSA. However, the social and medical morbidities of a permanent tracheostomy and the advent of surgical alternatives

have made tracheostomy an unpopular solution to OSA, reserved for those patients with the most severe sleep apnea not manageable by other interventions.

Laser-assisted uvulopalatoplasty (LAUP) is an outpatient surgical procedure, which has been used as a treatment for snoring. LAUP has also been used as a treatment for sleep-related breathing disorders, including obstructive sleep apnea. The American Academy of Sleep Medicine Standards of Practice Committee reviewed the evidence supporting the use of LAUP in obstructive sleep apnea, and found that adequate controlled studies on the LAUP procedure for sleep-related breathing disorders were not found in the peer-reviewed literature (Littner et al, 2001). The AASM concluded that "LAUP is not recommended for treatment of sleep-related breathing disorders."

There is some evidence for the use of uvulectomy or uvuloplasty as a treatment for snoring, but Aetna does not consider treatment of snoring medically necessary because snoring, in itself, is not associated with functional limitations. Most of the published literature on uvulectomy have to do with ritual removal of the uvula at birth in Africa, a practice that is associated with significant complications. Uvulectomy is also performed, again primarily in Africa, as a treatment for recurrent throat infections. However, there is no reliable evidence to support this practice. Acute edema of the uvula causing respiratory distress is an accepted indication for uvulectomy. Hawke and Kwok (1987) reported on uvulectomy in treating a patient with acute inflammatory edema of the uvula (uvulitis) associated with asphyxiation. Waeckerle et al (1976) reported on uvulectomy for hereditary angioneurotic edema. There is no evidence to support the use of uvulectomy as a treatment for gagging. Dawodu (2007) reported that gagging may occur as a complication of uvulectomy.

An UpToDate review on "Surgical treatment of obstructive sleep apnea in adults" (Weaver and Kapur, 2017) state that surgery can play a role in the management of selected patients who fail or do not tolerate CPAP therapy. Uvulopalatopharyngoplasty (UPPP) and UPPP are the most common surgical procedures for OSA, due to the upper pharyngeal obstruction which is the most common anatomic airway abnormality. The authors note that although UPPP frequently improves the physiologic abnormality of OSA, as well as clinical symptoms, the degree of

polysomnographic benefit is variable, and cures are rare. "Simple tonsillectomy in selected patients with tonsillar hypertrophy and otherwise favorable anatomy (eg, small tongue) is associated with a high rate of success."

An UpToDate review on "Tonsillectomy in adults: Indications" (Busaba and Doron, 2015) states that CPAP is initially tried before tonsillectomy. For individuals with asymmetric tonsils, tonsillectomy would be indicated when the individual also has concurrent signs or symptoms suggesting possible malignancy (e.g., chronic pain, dysphagia, mucosal abnormality, persistent cervical adenopathy, progressive tonsillar enlargement, and/or systemic symptoms). The authors note that tonsillar hypertrophy can cause or contribute to obstructive sleep apnea (OSA). The authors further note that, for most adults, "first-line treatment for OSA is weight loss (if appropriate), sleep hygiene, and continuous positive airway pressure. Tonsillectomy may be part of a surgical treatment protocol, usually combined with uvulopalatopharyngoplasty."

Adil (2017) discuss uvulopalatopharyngoplasty indications. The authors state that UPPP is most common surgery performed for adults with OSA in the U.S.. They report that UPPP surgery can be considered if a patient is unable to tolerate CPAP therapy. They further note general indications for surgical intervention to include mild obstructive sleep apnea with excessive daytime fatigue, an apnea-hypopnea index of 15 or more, oxyhemoglobin desaturation less than 90%, and/or cardiac arrhythmias associated with obstructions.

Radiofrequency ablation may be used to reduce and tighten excess tissues of the soft palate, uvula and tongue base (Somnoplasty) or nasal passages and soft palate (Coblation or Coblation channeling). These procedures are performed in an outpatient setting under local anesthesia. Current literature does not support their efficacy and applicability for OSA. Most published studies have been nonrandomized and have enrolled highly selected patients. These studies also fail to report long-term outcomes or recurrence rates. Woodson et al (2003) reported on the results of radiofrequency ablation of the turbinates and soft palate in patients with mild to moderate obstructive sleep apnea (AHI of 10 to 30 on screening sleep study). A total of 90 subjects were randomly assigned to radiofrequency ablation, CPAP, or sham-placebo. Subjects assigned to radiofrequency ablation had a moderate decrease in AHI that did not reach statistical significance. The AHI of subjects assigned to radiofrequency ablation decreased by an

average of 4.5 events/hour, whereas the AHI of subjects assigned to sham-placebo decreased by an average of 1.8 events/hour, a difference that did not achieve statistical significance. However, compared with sham-placebo, subjects assigned to radiofrequency ablation reported statistically significant improvements in quality of life, airway volume, apnea index and respiratory arousal index. In addition to the modest impact of radiofrequency ablation on AHI, this study has a number of other important limitations. First, it is a relatively small study, and improvements were not consistently seen among each of the measured parameters. Second, a significant number of subjects were lost to follow-up, and data were incomplete on 25 % of study subjects. Third, the study does not report on long-term clinical outcomes or recurrence rates. Fourth, although this study did not involve a direct comparison with UPPP, which is the current surgical standard treatment for OSA, studies of UPPP have reported much more substantial improvements in AHI, AI and other relevant parameters. Finally, this study involved a single investigator group and is the only published randomized clinical study of radiofrequency ablation for OSA; this study needs to be replicated by other investigators and in larger numbers of subjects.

A recent study (Garrigue et al, 2002) reported on the results of an uncontrolled case series examining the impact of atrial overdrive pacing in 15 patients with central or OSA syndrome who had received permanent atrial-synchronous ventricular pacemakers for symptomatic sinus bradycardia. With atrial overdrive pacing, achieved by increasing the atrial base rate, patients had a significantly reduced the number of episodes of central or OSA (from an average AHI of 28 with spontaneous rhythm to an average AHI of 11 with atrial overdrive pacing) without a significant reduction in total sleep time. The authors, however, concluded that further studies are needed to elucidate the mechanisms involved in achieving these reductions and to assess the precise role of cardiac pacing in preventing symptoms, disability, and death in patients with sleep apnea syndrome. In a randomized controlled trial, Luthje et al (2005) aimed to reproduce the finding of a recent study that atrial overdrive pacing markedly improved SDB. These investigators found that neither the primary endpoint AHI, nor the apnea index, oxygen desaturation, ventilation, biomarkers were affected by the nocturnal atrial overdrive pacing. They concluded that the lack of effect on the AHI means that atrial overdrive pacing is inappropriate for treating SDB. This is in agreement with the findings of a randomized controlled study by Pepin et al (2005) who reported that atrial overdrive pacing has no significant effect on OSA.

In a randomized controlled study, Simantirakis et al (2005) reported that atrial over-drive pacing had no significant effect in treating OSA-hypopnea syndrome. In another randomized controlled study, Krahn et al (2006) evaluated the impact of prevention of bradycardia with physiologic pacing on the severity of OSA. The authors concluded that temporary atrial pacing does not appear to improve respiratory manifestations of OSA, and that permanent atrial pacing in this patient population does not appear to be justified.

Upper airway resistance syndrome (UARS) is characterized by a normal AHI, but with sleep fragmentation related to subtle airway resistance. With UARS, cessation of breathing does not occur nor does a decrease in oxygen saturation, as with apneas and hypopneas. Guilleminault and colleagues (1993) considered UARS clinically significant if it entails greater than 10 episodes of EEG arousals/hour of sleep in patients with a documented history of excessive daytime sleepiness. They described UARS as multiple sleep fragmentations resulting from very short alpha EEG arousals, which in turn are related to an increase in resistance to airflow. According to Guilleminault et al (1993), the resistance to airflow is subtle enough that it is not detected by routine sleep analysis, but can be detected with esophageal pressure tracings. In addition, UARS may not be associated with snoring, the classic symptom of OSA. However, there is no consensus on the criteria for diagnosis or indications for treatment of UARS. Neither the American Sleep Disorders Association nor any other professional medical organization has issued guidelines for the diagnosis and treatment of UARS.

Cautery-assisted palatal stiffening operation (CAPSO) is an office-based procedure performed with local anesthesia for the treatment of palatal snoring. A midline strip of soft palate mucosa is removed, and the wound is allowed to heal by secondary intention. The flaccid palate is stiffened, and palatal snoring ceases. Wassmuth et al (2000) evaluated the ability of CAPSO to treat OSA syndrome (OSAS). A total of 25 consecutive patients with OSAS underwent CAPSO.

Responders were defined as patients who had a reduction in AHI of 50 % or more and an AHI of 10 or less after surgery. By these strict criteria, 40 % of patients were considered to have responded to CAPSO. Mean AHI improved significantly from 25.1 ± 12.9 to 16.6 ± 15.0 . The Epworth Sleepiness Scale improved significantly from 12.7 ± 5.6 to 8.8 ± 4.6 . Mair and Day (2000) analyzed data on CAPSO with regard to extent of surgery, need for repetition of procedure, results, complications, predictors of success. A total of 206 consecutive patients

underwent CAPSO over an 18-month period, followed by office examination and telephone evaluation. The success rate was initially 92 % and dipped to 77 % after 1 year. CAPSO eliminates excessive snoring caused by palatal flutter and has success rates that were comparable with those of traditional palatal surgery. The authors stated that CAPSO is a simple and safe office procedure that avoids the need for multiple-stage operations and does not rely on expensive laser systems or radiofrequency generators and hand pieces. The results of these studies appear to be promising; however their findings need to be verified by randomized controlled studies.

In a prospective, non-randomized study, Pang and Terris (2007) evaluated the effectiveness of CAPSO in treating snoring and mild OSA. A total of 13 patients with simple snoring and mild OSA underwent the modified CAPSO under local anesthesia. Patients had pre-operative polysomnography and at 3 months post-operatively; they were Friedman stage II and III, with tonsil size 0, 1, or 2. All patients had improvement in their snoring; 84 % had improvement in the Epworth Sleepiness Scale, from 12.2 to 8.9. Objective success on the polysomnogram was noted in 75 % of patients (6/8) with mild OSA. The AHI improved from 12.3 % to 5.2 % ($p < 0.05$), and the lowest oxygen saturation improved from 88.3 % to 92.5 % ($p < 0.05$). The authors concluded that the modified CAPSO is a simple, low-cost, and effective office-based method to treat snoring and mild OSA. The findings of this small study are promising. Randomized controlled trials with larger sample size and longer follow-up are needed to ascertain the clinical value of CAPSO.

The Pillar Palatal Implant System (Restore Medical, Inc.) is intended as a treatment option for snoring and OSA. The System consists of an implant and a delivery tool. The implants are designed to stiffen the tissue of the soft palate reducing the dynamic flutter which causes snoring. According to the manufacturer, the implants reduce the incidence of airway obstruction caused by the soft palate. The implant is a cylindrical shaped segment of braided polyester filaments. The delivery tool is comprised of a handle and needle assembly that allows for positioning and placement of the implant submucosally in the soft palate. The implant is designed to be permanent while the delivery tool is disposable.

Clinical information on Restore's website reported that with the Pillar Procedure, AHI was reduced in 13 of 16 patients (81.3 %) with a 53.4 % mean decrease for those 13 patients. Six of the 13 patients (46.2 %) experienced an AHI decrease of greater than 50 % along with a 90-day AHI of less than 10. Ten of the 13 patients (76.9 %) decreased to an AHI less than 10. While these data appeared promising, larger prospective clinical studies with longer follow-up are needed in the peer-reviewed published literature to validate the effectiveness of this procedure for OSA.

In a retrospective review of 125 patients who underwent the Pillar implant for snoring and obstructive sleep apnea/hypopnea syndrome (OSAHS), Friedman and colleagues (2006) found that the Pillar implant is an effective treatment for snoring and OSAHS in selected patients and can be combined with adjunctive procedures to treat OSAHS. The major drawback of this study was that it was a short-term study. Well-designed studies with long-term follow-up are needed to determine the real value of this technique.

A structured assessment of the evidence for the Pillar procedure by Adelaide Health Technology Assessment for the Australian Department of Health and Ageing (Mundy et al, 2006) concluded: "Further investigation is required to establish which patients (mild or moderate obstructive sleep apnoea) would benefit the most from this procedure, and whether greater success would be achieved in conjunction with more invasive surgical procedures. In addition, long-term follow-up of obstructive sleep apnea patients may indicate whether or not the observed reductions in AHI delivered a clinical benefit to these patients".

This is in agreement with the conclusions of an assessment by the Canadian Agency for Drugs and Technologies in Health (CADTH, 2007), which stated that there is currently insufficient published evidence to ascertain if palatal implants (e.g., the Pillar System) are an effective treatment option for patients with mild to moderate OSA due to palatal obstruction. The CADTH report further stated that larger, randomized controlled studies are needed to determine the long-term safety and effectiveness of the implants in a more diverse patient population, including those who are obese or those with co-morbid medical conditions. Comparisons with existing treatments for OSA are also needed.

An assessment by the National Institute for Health and Clinical Excellence (NICE, 2007) reached similar conclusions about the lack of reliable evidence of the effectiveness of palatal implants as a treatment for obstructive sleep apnea. The assessment concluded: "Current evidence on soft-palate implants for obstructive sleep apnoea (OSA) raises no major safety concerns, but there is inadequate evidence that the procedure is efficacious in the treatment of this potentially serious condition for which other treatments exist. Therefore, soft-palate implants should not be used in the treatment of this condition".

In a prospective study, Nordgard et al (2007) assessed the long-term effectiveness of palatal implants for treatment of mild-to-moderate OSA. A total of 26 referred patients with a pre-treatment AHI of 10 to 30 and a BMI of less than or equal to 30, representing an extended follow-up of a subset of 41 patients enrolled in previous short-term trials were included. Twenty-one of 26 patients (80.8 %) experienced a decrease in AHI. Fifteen of 26 patients (57.7 %) had a follow-up AHI less than 10 at 1 year, whereas 13 patients (50 %) had a 50 % or greater reduction to an AHI less than 10 at 1 year. Mean AHI was reduced from 16.5 +/- 4.5 at baseline to 12.5 +/- 10.5 at 3 months ($p < 0.014$) and to 12.3 +/- 12.7 at 1 year ($p < 0.019$). The authors concluded that patients initially responding to palatal implants with improved AHI maintained improvement through long-term follow-up at 1 year. The main drawback of this study was its small sample size. The authors noted that additional studies with longer follow-up would be appropriate.

In a continuation of a prospective case series, Walker et al (2007) assessed the long-term safety and outcomes of palatal implants for patients with mild-to-moderate OSA. Polysomnography, daytime sleepiness, and snoring intensity were measured at baseline, 90 days, and extended follow-up. A total of 22 (42 %) patients from the previous study were followed for a median of 435.5 days. Thirteen were classified as responders, based on their 90-day evaluation; 76.9 % of initial responders maintained improvements in AHI, daytime sleepiness, and snoring at extended follow-up. Nine patients were initial non-responders for AHI and daytime sleepiness and remained unchanged at extended follow-up. However, snoring for these 9 patients initially improved, and the improvement continued through extended follow-up. The authors concluded that initial response or non-response to palatal implants remains stable over an extended period. However, they noted that the generalizability of these results is unknown because of significant

loss to follow-up (31 of 53 or 58 %). Other drawbacks of this study were small sample size, lack of randomization, as well as selection bias that can occur among patients who chose to participate in a follow-up study.

In a multi-institution, randomized, placebo-controlled study, Steward and colleagues (2008) examined the effectiveness of Pillar palate implants for OSA. A total of 100 patients with mild-to-moderate OSA and suspected retropalatal obstruction were randomly assigned treatment with three palatal implants or sham placebo. Final AHI increased for both groups at 3 months, correlating with increased percentage of supine sleep but was less in the implant group ($p = 0.05$). A clinically meaningful reduction in AHI (greater than or equal to 50 % reduction to less than 20) was more common in the implant group (26 % versus 10 %, $p = 0.05$). Significant differences were noted for changes in lowest oxyhemoglobin saturation ($p = 0.007$) and Functional Outcomes of Sleep Questionnaire ($p = 0.05$). Improvement in Epworth Sleepiness Score did not differ from that of sham ($p = 0.62$). Partial implant extrusion occurred in 2 patients (4 %). The authors concluded that palate implants for mild-to-moderate OSA showed effectiveness over placebo for several important outcomes measures with minimal morbidity, but overall effectiveness remains limited. They stated that further study is needed.

In a randomized, double-blind, placebo-controlled study, Gillespie et al (2011) examined if the Pillar palatal implant system reduces CPAP pressure and improves patient compliance with CPAP therapy. Subjects with mild-to-moderate sleep apnea dissatisfied with CPAP because of pressure-related complaints were randomized to receive Pillar implants or a sham procedure performed in double-blind fashion. Active and sham groups were compared for changes in therapeutic CPAP pressures (primary outcome) with a 90-day follow-up sleep study and CPAP compliance (secondary outcome) with a 90-day smart card report. A total of 26 subjects were randomized to Pillar implants and 25 to a sham implant procedure. There were no differences between groups with regard to demographics and baseline parameters. Both sham and active groups had reduced mean CPAP pressure (-1.1 versus -0.5 cm H₂O) with no difference between groups ($p = 0.32$) at 90-day follow-up. In addition, there was no difference in average daily CPAP use between groups ($p = 0.80$). Both groups experienced improvements in Epworth sleepiness scores and Functional Outcome of Sleep Questionnaire scores at 90 days with no differences between groups. The active group reported significantly higher CPAP satisfaction

scores than the sham group ($p = 0.04$). The authors concluded that Pillar implants do not significantly reduce CPAP pressure or increase CPAP compliance compared to sham controls but marginally improve subjective CPAP satisfaction (but the reason for this is unclear). These findings do not presently support the use of Pillar implants as an adjunctive treatment to improve CPAP compliance.

In a Cochrane review, Smith et al (2006) ascertained the effectiveness of drug therapies in the treatment of OSA. The authors concluded that there is insufficient evidence to recommend the use of drug therapy in the treatment of OSA. They noted that small studies have reported positive effects of certain agents on short-term outcome. Certain agents have been shown to reduce the AHI in largely unselected populations with OSA by between 24 and 45 %. For fluticasone, mirtazipine, physostigmine and nasal lubricant, studies of longer duration are needed to establish if this has an impact on daytime symptoms. Individual patients had more complete responses to particular drugs. It is likely that better matching of drugs to patients according to the dominant mechanism of their OSA will lead to better results and this also requires more investigation.

Transpalatal advancement pharyngoplasty (TAP) changes the retro-palatal airway by advancing the palate forward without excising the soft palate. The TAP procedure has been employed alone or in combination with other soft tissue surgeries for patients with narrowing in the retro-palatal airway, in particular, narrowing proximal to the point of palatal excision using traditional UPPP techniques. A transpalatal approach and advancement has also been advocated for individuals with obstructions in the nasopharynx that can not be accessed through traditional techniques. However, to date, there is very little published outcomes data for patients with OSA. Woodson (2005) described the findings of 30 subjects who underwent TAP; 20 of them also had various tongue-base procedures performed at the same time as TAP. Only 10 had TAP alone. Post-operative AHI in these 30 patients was better than a comparable group of 44 patients undergoing UPPP, 26 of whom had UPPP as the sole procedure. In addition, for the patients in each group who did not have additional tongue base surgery, the AHI improved significantly more in the TAP-treated subjects ($n = 10$) than the UPPP-treated subjects ($n = 26$). Larger studies are needed to establish the safety and effectiveness of the TAP procedure, together with prospective comparisons with established palate-based surgical techniques.

It has been suggested that nasal surgery may improve subjective daytime complaints in patients with OSA. However, published reports have not demonstrated that reducing nasal obstruction and resistance from various causes and using various methods, (e.g., polypectomy, septoplasty, turbinectomy, and radiofrequency ablation of inferior nasal turbinates) correlates with a significant reduction in objective OSA indicators (e.g., AHI or nocturnal oxygen desaturation). In this regard, Kohler and colleagues (2007) stated that the impact of treating nasal obstruction in patients with snoring and OSA on long-term outcome remains to be defined through randomized controlled studies of medical as well as surgical treatments.

Koutsourelakis et al (2008) stated that although nasal surgery has limited effectiveness in OSA treatment, some patients experience improvement. These researchers tested the hypothesis that post-surgery improvement is associated with increased nasal breathing epochs. A total of 49 OSA patients (mean AHI 30.1 +/- 16.3 events x h(-1)) with symptomatic fixed nasal obstruction due to deviated septum were randomly assigned to either septoplasty (surgery group; n = 27) or sham surgery (placebo group; n = 22). The breathing route was examined during over-night polysomnography. All patients in the placebo group were non-responders, whereas in the surgery group 4 (14.8 %) patients were responders and exhibited considerable increase in nasal breathing epochs (epochs containing more than 3 consecutive phasic nasal signals), and 23 patients were non-responders, presenting a modest increase in nasal breathing epochs. The change in AHI was inversely related to the change in nasal breathing epochs, with responders exhibiting among the greatest increases in nasal breathing epochs. Baseline nasal breathing epochs were positively related to percent change in AHI. Responders had among the lowest baseline nasal breathing epochs; a cut-off value of 62.4 % of total sleep epochs best separated (100 % sensitivity, 82.6 % specificity) responders/non-responders. The authors concluded that nasal surgery rarely treats OSA effectively; but baseline nasal breathing epochs can predict the surgery outcome.

Lin and associates (2008) provided an overview of the literature on multi-level surgery for patients with OSA/hypopnea syndrome (OSAHS) patients. Articles were included only if the surgical intervention involved at least two of the frequently involved anatomical sites: nose, oropharynx, and hypopharynx. After applying specific inclusion criteria, 49 multi-level surgery articles (58 groups) were identified. There were 1,978 patients included in the study. The mean minimal

follow-up time was 7.3 months (range of 1 to 100 months). A meta-analysis was performed to re-define the success rate to be consistent with the commonly agreed upon criteria, namely "a reduction in the AHI of 50 % or more and an AHI of less than 20". "Success" implies an improved condition and is not meant to imply cure. The re-calculated success rate was 66.4 %. The overall complication rate was 14.6 %. The evidence-base medicine (EBM) level of these 49 studies revealed that only 1 study was EBM level 1, 2 papers were EBM level 3, and the other 46 papers were ranked as level 4 evidence. The authors concluded that multi-level surgery for OSAHS is associated with improved outcomes, although this benefit is supported largely by level 4 evidence. They stated that future research should focus on prospective and controlled studies.

This is in agreement with the observation of Randerath et al (2007) who noted that combined surgeries in the sense of multi-level surgery concepts are of increasing interest in the secondary treatment of OSA following failure of nasal ventilation therapy although more evidence from prospective controlled trials are needed.

In a prospective, randomized cross-over study, Thomas et al (2003) compared the effectiveness of 2 tongue-base surgical procedures in the treatment of patients with moderate-to-severe sleep-disordered breathing. A total of 17 patients with moderate-to-severe sleep-disordered breathing and Fujita type II upper airway collapse for whom conservative treatment failed were enrolled in this study. They were randomly assigned to undergo palatopharyngoplasty combined with either tongue advancement (mandibular osteotomy) or tongue suspension. Parameters assessed included severity of sleep-disordered breathing (polysomnography), sleepiness (Epworth Sleepiness Scale [ESS]), and anatomic changes (upper airway endoscopy), as well as demographic factors. Patients not achieving satisfactory improvement in their condition were offered non-surgical management or additional surgical treatment that varied based on the post-operative assessment but included crossing-over to the other tongue surgical procedure. Nine of the 17 patients were randomized to the tongue suspension group, and 8 to the tongue advancement group. In the 9 tongue suspension patients, ESS scores fell from 12.1 to 4.1 ($p = 0.007$). Airway collapse for all 9 patients measured on Müller maneuver improved, by a mean of 64 % ($p = 0.0006$) at the palate and 83 % ($p = 0.0003$) at the base of the tongue. In the 8 tongue advancement patients, ESS scores fell from a mean of 13.3 to 5.4 ($p = 0.004$). Airway collapse for 5 of 8 patients measured on Müller maneuver improved by a mean of 31 % ($p = 0.1$) at the palate and 75 % ($p = 0.03$) at the base of the tongue. The authors concluded that prospective,

randomized trials of tongue-base surgery for sleep-disordered breathing are possible. Preliminary findings from the current protocol reveal a slight advantage of tongue suspension over tongue advancement.

In a Cochrane review on surgery for OSA that included tongue advancement and tongue suspension, Sundaram et al (2005) concluded that the review do not provide evidence to support the use of surgery in sleep apnea/hypopnea syndrome, as overall significant benefit has not been demonstrated. Subjects recruited to the studies had mixed levels of AHI, but tended to suffer from moderate daytime sleepiness where this was measured. Short-term outcomes are unlikely to consistently identify suitable candidates for surgery. Long-term follow-up of individuals who undergo surgical correction of upper airway obstruction is needed. This would help to determine whether surgery is a curative intervention, or whether there is a tendency for the signs and symptoms of sleep apnea to re-assert themselves, prompting patients to seek further treatment for sleep apnea.

In a pilot study, Hamans et al (2008) examined the effectiveness of adjustable tongue advancement for the treatment of OSA. A total of 10 patients (mean age of 44 years) with moderate-to-severe OSA, i.e., an AHI between 15 and 50, with CPAP intolerance were included in this prospective, non-randomized, multi-center study to evaluate the feasibility, safety, and effectiveness of this novel procedure, which consists of the implantation of a tissue anchor in the tongue base and an adjustment spool at the mandible. Titration of this tissue anchor results in advancement of the tongue and a patent upper airway. The mean AHI decreased from 22.8 at baseline to 11.8 at the 6-month follow-up ($p = 0.007$). The ESS score decreased from 11.4 at baseline to 7.7 at the 6-month follow-up ($p = 0.094$), and the snoring score decreased from 7.5 at baseline to 3.9 at the 6-month follow-up ($p = 0.005$). Four technical adverse events were noted, and 1 clinical adverse event occurred. The authors concluded that adjustable tongue advancement is a feasible and relatively safe way to reduce the AHI and snoring in selected patients with moderate-to-severe OSA and CPAP intolerance. Technical improvements and refinements to the procedure are ongoing.

In a phase II, prospective, multi-center, case series study, Woodson and colleagues (2010) examined the safety and effectiveness of a new surgical device for tongue suspension for OSA -- the Advance System (an adjustable tongue-advancement device). Surgically naive patients with moderate-to-severe OSA and tongue base obstruction (BMI less than 32, AHI 15 to 60) underwent surgical insertion of a mid-line tissue anchor into the posterior tongue and connected to an adjustable mandibular bone anchor with a flexible tether. Outcomes included changes in AHI, sleepiness (Epworth Sleepiness Scale), sleep-related quality-of-life (Functional Outcomes of Sleep Questionnaire), snoring, swallowing, speech, and pain (0 to 10 visual analog scale [VAS]). Following implantation of the device, 42 patients (mean age of 50 years, BMI 28) noted improvement at 6 months for AHI (mean [SD]: 35.5 [20.4] to 27.3 [18.8]), Epworth Sleepiness Scale (11.5 [3.9] to 7.8 [4.7]), and Functional Outcomes of Sleep Questionnaire (15.5 [2.6] to 17.5 [2.6], all $p < 0.01$). Snoring VAS scores improved (7.3 [2.1] to 4.7 [2.9], $p < 0.01$). Post-implantation pain scores were mild-to-moderate (4.4) at day 1 and resolved by day 5. Post-titration pain scores were mild (less than 2). Device-related adverse events included wound infection (7 %) and edema or seroma (5 %), which resolved. However, in 31 % of patients, asymptomatic tissue anchor barb fractures were observed radiographically. The authors concluded that the tissue anchor failure rate of the tested device precludes its clinical use; however, the study results support that a titratable, tongue-suspension device with low direct surgical morbidity in patients with moderate-to-severe OSA significantly improves multiple measures of sleep apnea. They stated that further investigation is warranted.

Obstructive sleep apnea has been reported to be common in medically refractory epileptic patients. Chihorek and colleagues (2007) examined if OSA is associated with seizure exacerbation in older adults with epilepsy. Polysomnography was performed in older adult patients with late-onset or worsening seizures (group 1, $n = 11$) and those who were seizure-free or who had improvement of seizures (group 2, $n = 10$). Patients in group 1 had a significantly higher AHI than patients in group 2 ($p = 0.002$). Group 1 patients also had higher Epworth Sleepiness Scale scores ($p = 0.009$) and higher scores on the Sleep Apnea Scale of the Sleep Disorders Questionnaire ($p = 0.04$). The two groups were similar in age, BMI, neck circumference, number of anti-epileptic drugs currently used, and frequency of nocturnal seizures. The authors concluded that OSA is associated with seizure exacerbation in older adults with epilepsy, and its treatment may represent an important avenue for improving seizure control.

in this population. Moreover, they noted that large, prospective, placebo-controlled studies are needed to ascertain if treatment of OSA (e.g., CPAP) improves seizures control in patients with epilepsy.

Malow and colleagues (2008) stated that small, uncontrolled case series suggested that treatment of OSA in patients with epilepsy may improve seizure control. These researchers addressed critical design issues in a pilot study before conducting a definitive, randomized, controlled trial. They identified a cohort of adult patients with medically refractory epilepsy and co-existing OSA, documented by PSG. After an 8-week baseline period, subjects with OSA were randomized to therapeutic or sham CPAP for 10 weeks. Subjects maintained seizure calendars and anti-epileptic drug dosages were held constant. A total of 68 subjects with suspected OSA were enrolled and 35 subjects randomized to therapeutic CPAP ($n = 22$) or sham CPAP ($n = 13$). Male gender and an elevated sleep apnea questionnaire score were predictive of OSA on PSG. Nineteen subjects in the therapeutic group and all 13 subjects in the sham group completed the trial. Baseline AHI and CPAP adherence were comparable between groups. A significant reduction in AHI was observed in the therapeutic CPAP group as compared to the sham group. Subjects, study co-ordinators, and principal investigators were unable to predict treatment allocation. The authors concluded that the findings of this pilot study provided critical information related to study design and feasibility for planning a comprehensive trial to test the hypothesis that treating OSA in patients with epilepsy improves seizure control. They stated that randomized, large-scale, multi-center clinical trials are needed to confirm these results.

The Provent sleep apnea therapy is a non-invasive treatment for OSA. The Provent nasal device uses a novel MicroValve design that attaches over the nostrils and is secured in place with hypo-allergenic adhesive. The MicroValve opens and closes, redirecting air through small holes to create resistance upon breathing out.

In a pilot study, Colrain and associates (2008) tested the hypothesis that the application of expiratory resistance via a nasal valve device would improve breathing during sleep in subjects with OSA and in primary snorers. A total of 30 men and women were recruited from the community and from the Stanford University Sleep Disorders Clinic; 24 had at least mild OSA (AHI greater than 5), and 6 were primary snorers. Subjects underwent 2 nights of

polysomnographic evaluation, one with and one without a new nasal resistance device with the order of nights counter-balanced across participants. The device consisted of a small valve inserted into each nostril calibrated to provide negligible inspiratory resistance, but increased expiratory resistance with a back pressure between 60 and 90 cm H₂O*sec/Liter (at 100 ml/sec flow). Standard PSG was conducted to compare participants' sleep both with and without the device, with the scoring conducted blind to treatment condition. The AHI ($p < 0.001$) and oxygen desaturation (O₂DI) ($p < 0.01$) indices both significantly decreased, and the percentage of the night spent above 90 % saturation ($p < 0.05$) significantly increased with device use. The observed amount of snoring ($p < 0.001$) was significantly decreased with device use, and there were no significant changes in measures of sleep architecture. The authors concluded that these findings were suggestive of a therapeutic effect of expiratory nasal resistance for some OSA patients and indicated that this technique is worthy of further clinical study. This trial examined the effect of the device over 1 day, and thus did not provide any information on the durability of the effect of the device in OSA.

In a multi-center study, Rosenthal et al (2009) evaluated the effectiveness of a novel device placed in the nares that imposes an expiratory resistance for the treatment of OSA and assessed adherence to the device over a 30-day in-home trial period. One diagnostic and 3 treatment polysomnograms were administered in a Latin-square design to identify the optimal expiratory resistance to be used during the 30-day in-home trial. Subjects had repeat PSG with the prescribed device at the end of the 30-day trial. Subjects ($n = 34$; aged 27 to 67 years) with a baseline AHI greater than or equal to 5 were included in this study. The AHI was reduced from 24.5 +/- 23.6 (mean +/- SD) to an average of 13.5 +/- 18.7 ($p < 0.001$) across initial treatment nights. The AHI was 15.5 +/- 18.9 ($p = 0.001$) for the prescribed device at the end of the 30-day trial. Of 24 subjects with an AHI greater than 10 at baseline, 13 achieved an AHI less than 10 on the initial treatment nights; 10 had a similar response on the final treatment night. Percent of the night snoring decreased from 27.5 +/- 23.2 to 11.6 +/- 13.7 ($p < 0.001$) on initial treatment nights and 14.6 +/- 20.6 ($p = 0.013$) at the end of the trial; Epworth Sleepiness scores decreased from 8.7 +/- 4.0 at baseline to 6.9 +/- 4.4 ($p < 0.001$) at the end of the trial; the Pittsburgh Sleep Quality Index improved from 7.4 +/- 3.3 to 6.5 +/- 3.6 ($p = 0.042$). Mean oxygen saturation increased from 94.8 +/- 2.0 to 95.2 +/- 1.9 ($p = 0.023$) on initial treatment nights and 95.3 +/- 1.9 ($p = 0.003$) at the end of the trial. Sleep architecture was not affected. Participants reported using the device

all night long for 94 % of nights during the in-home trial. The authors concluded that treatment with this novel device was well-tolerated and accepted by the participants. An overall reduction in AHI was documented; however, therapeutic response was variable among the participants. They stated that further research is needed to identify the ideal candidates for this new therapeutic option in the management of OSA. This small, uncontrolled trial, which showed a statistically significant impact on one of the primary endpoints, AHI, but a non-significant result for another endpoint, oxygen desaturation index. In addition, Provent has not been either compared to CPAP, or evaluated in persons who have failed CPAP. Although reduction in AHI with Provent was significant, patients on average still had clinically significant OSA (AHI greater than 5); by contrast, studies of CPAP have shown success in getting AHI below 5.

Walsh et al (2011) evaluated the short-term efficacy of and adherence with a convenient expiratory positive airway pressure (EPAP) nasal device was evaluated in OSA patients non-adherent with CPAP. Participants were OSA patients who refused CPAP or used CPAP less than 3 hrs/night. After demonstrating tolerability to the EPAP device during approximately 1 week of home use, patients underwent a screening/baseline polysomnogram (PSG1) and a treatment PSG (PSG2). Patients meeting pre-specified efficacy criteria underwent PSG3 after about 5 weeks of EPAP treatment. Forty-seven of 59 eligible patients (80 %) tolerated the device and underwent PSG1. Forty-three patients (27 males, 16 females; 53.7 ± 10.9 years) met apnea-hypopnea index (AHI) entry criteria and underwent PSG2. Mean AHI decreased from 43.3 ± 29.0 at baseline to 27.0 ± 26.7 ($p < 0.001$) at PSG2. Twenty-four patients (56 %) met efficacy criteria; their mean AHI was 31.9 ± 19.8 , 11.0 ± 7.9 , 16.4 ± 12.2 at PSG1, PSG2, and PSG3, respectively ($p < 0.001$, PSG1 versus both PSG2 and PSG3). Mean Epworth Sleepiness Scale (ESS) scores were 12.3 ± 4.8 at baseline, 11.1 ± 5.1 at PSG1, and 8.7 ± 4.4 at PSG3 ($p = 0.001$ compared to baseline). Device use was reported an average of 92 % of all sleep hours. The authors concluded that the improvements in AHI and ESS, combined with the high degree of treatment adherence observed, suggested that the convenient EPAP device tested may become a useful therapeutic option for OSA. Limitations of this study included lack of a sham or other comparative treatment, lack of objective method for measuring adherence data, small sample size and short duration of study, as well as frequent interaction by study staff.

Berry et al (2011) examined the efficacy of a novel nasal expiratory positive airway pressure (EPAP) device as a treatment for OSA. Patients were treated with a nasal EPAP device (n = 127) or similar appearing sham device (n = 123) for 3 months. Polysomnography (PSG) was performed on 2 non-consecutive nights (random order: device-on, device-off) at week 1 and after 3 months of treatment. Analysis of an intention- to-treat group (ITT) (patients completing week 1 PSGs) (EPAP n = 119, sham n = 110) was performed. At week 1, the median AHI value (device-on versus device-off) was significantly lower with EPAP (5.0 versus 13.8 events/hr, p < 0.0001) but not sham (11.6 versus 11.1 events/h, p = NS); the decrease in the AHI (median) was greater (-52.7 % versus -7.3 %, p < 0.0001) for the ITT group. At month 3, the percentage decrease in the AHI was 42.7 % (EPAP) and 10.1 % (sham), p < 0.0001. Over 3 months of EPAP treatment the Epworth Sleepiness Scale decreased (9.9 ± 4.7 to 7.2 ± 4.2 , p < 0.0001), and the median percentage of reported nights used (entire night) was 88.2 %. The authors concluded that nasal EPAP device significantly reduced the AHI and improved subjective daytime sleepiness compared to the sham treatment in patients with mild to severe OSA with excellent adherence. The results of this study suggested that nasal EPAP is an effective treatment alternative for a substantial percentage of OSA patients. Limitations of this study included large number of exclusion criteria, and lack of objective method for measuring adherence data. Also, no baseline predictors of treatment success were identified by post hoc analysis.

Patel et al (2011) examine characteristics predictive of therapeutic response to the device and provided pilot data as to its potential mechanisms of action. A total of 20 subjects (15 males, 5 females, aged 54 ± 12 years, BMI 33.5 ± 5.6 kg/m²) with OSAHS underwent 3 nocturnal polysomnograms (NPSG) including diagnostic, therapeutic (with a Provent® nasal valve device), and CPAP. Additional measurements included intra-nasal pressures and PCO₂, closing pressures (Pcrit), and awake lung volumes in different body positions. In 19/20 patients who slept with the device, RDI was significantly reduced with the nasal valve device compared to the diagnostic NPSG (27 ± 29 /hr versus 49 ± 28 /hr), with 50 % of patients having an acceptable therapeutic response. Among demographic, lung volume, or diagnostic NPSG measures or markers of collapsibility, no significant predictors of therapeutic response were found. There was a suggestion that patients with position-dependent SDB (supine RDI greater than lateral RDI) were more likely to have an acceptable therapeutic response to the device. Successful elimination of SDB was associated with generation and maintenance of an elevated end expiratory pressure.

No single definitive mechanism of action was elucidated. The authors concluded that the present study shows that the nasal valve device can alter SDB across the full spectrum of SDB severity.

There was a suggestion that subjects with positional or milder SDB in the lateral position were those most likely to respond (but this observation needs to be confirmed in a larger study). An important limitation of this study was that these researchers did not directly assess lung volume during sleep. The authors noted that this pilot study was not able to establish predictors of success or a single definitive mechanism of action; but does help define a restricted list of candidates for further investigation.

Kryger et al (2011) evaluated the long-term durability of treatment response and safety of a nasal EPAP device used to treat OSA. Patients in the EPAP arm of the EPAP versus sham randomized study who used the EPAP device \geq 4 hrs/night, \geq 5 nights/week on average during months 1 and 2 of the 3-month trial and had \geq 50 % reduction in AHI or AHI reduction to < 10 documented by polysomnography, comparing the 3-month device-on PSG to the week-one device-off PSG.

Treatment with a nasal EPAP device (n = 41) for 12 months. Polysomnography (PSG) on the patients wearing the device was performed after 12 months of treatment. The month 12 device-on PSG data from the analyzable subject cohort (n = 34) was compared to the week 1 device-off PSG from the EPAP versus sham trial. Of the 51 patients eligible, 34 were still using the EPAP device at the end of 12 months. Median AHI was reduced from 15.7 to 4.7 events/hr (week 1 device-off versus month 12 device-on). The decrease in the AHI (median) was 71.3 % ($p < 0.001$). The median proportion of sleep time with snoring was reduced by 74.4 % ($p < 0.001$).

Over 12 months of EPAP treatment, the Epworth Sleepiness Scale decreased (11.1 \pm 4.2 to 6.0 \pm 3.2, $p < 0.001$), and the median percentage of reported nights used (entire night) was 89.3 %.

The authors concluded that nasal EPAP significantly reduced the AHI, improved subjective daytime sleepiness and reduced snoring after 12 months of treatment. Long-term adherence to EPAP was excellent in those who had a positive clinical response at month 3 of the EPAP versus sham study. (This appeared to be the same study as reported by Berry et al, 2011 and exhibited similar limitations as that study).

The Zzoma positional device is a cervical pillow designed to prevent positional sleep apnea patients from rolling onto their backs. The device was cleared by the FDA based upon a 510(k) premarket notification due to its substantial equivalence to another positional device, a Sona

pillow, which is one of several cervical pillows that have been cleared for treatment of mild obstructive sleep apnea and snoring.

A number of studies have examined various positioning devices for treatment of positional obstructive sleep apnea. Skinner et al (2008) studied a thoracic anti-supine band (TASB), which mimics the ‘tennis-ball technique’ in a randomized cross-over trial of 20 adults with mild to moderate positional obstructive sleep apnea. Portable sleep studies measuring AHI were performed at start of treatment and at 1-month follow-up. Mean AHI (+/- SD) was 12.0 +/- 14.5/H for TASB and 4.9 +/- 3.9/H for nasal CPAP (nCPAP). No significant difference was found in sleep efficiency or subjective responses. The investigators concluded that “control of body position during sleep using an anti-supine device mimicking the so-called ‘tennis ball technique’ provides benefit in the management of position-dependent [obstructive sleep apnea hypopnea syndrome] in subjects who meet strict inclusion criteria. The overall improvement is, however, less than for nCPAP.

Lee et al (2009) evaluated optimal sleep positions in 16 patients, including lateral position, cervical vertebral support with head tilting (CVS-HT), scapula support (SS), and LP, through use of polysomnography for 2 successive nights. Lateral position was found to have the most dominant effect ($p = 0.0319$) and SS ($p = 0.0265$) for AHI. The study did not, however, specify any particular positional device for cervical support.

The Zzoma positional device has been examined in a clinical trial. Permut et al (2010) randomly assigned 38 patients to either the Zzoma positional device (PD) or CPAP. They found no significant difference between PD and CPAP in their ability to normalize their AHI ($p = 0.16$). However, the mean oxygen saturation (SaO₂) during the night was unchanged compared with baseline with the use of PD but was increased with CPAP therapy from 95 % to 96 % ($p < 0.001$). The lowest SaO₂ increased during the night for both PD and CPAP groups. The investigators concluded that positional therapy is equivalent to CPAP at normalizing the AHI in patients with positional OSA, with similar effects on sleep quality and nocturnal oxygenation. They noted that positional therapy is effective at maintaining sleep in the non-supine position during the night and is similar to CPAP therapy in its effects on sleep quality and nocturnal oxygenation. Whether more prolonged use will maintain these effects and how positional therapy compares with CPAP

in regard to cognitive function, compliance, and quality of life awaits further study. Drawbacks of this study included (i) it only studied the acute 1-night effects of the PD, as compared with CPAP. Assessment of effectiveness would require the use of other outcome measures, such as daytime sleepiness, cognitive function, and quality of life, all of which would have to be evaluated in a randomized trial after more prolonged use and would be influenced by compliance, and (ii) this study did not include patients with severe OSA.

No studies were found in the peer-reviewed literature comparing the Zzoma device to other positional devices. The Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep apnea in Adults released by the Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine (Epstein et al, 2009) state that "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". The guideline does not, however, specify a particular positional device. The guidelines state "[a] positioning device (e.g., alarm, pillow, back pack, tennis ball) should be used when initiating positional therapy".

Valbuza et al (2010) stated that treatment of OSA using methods for increasing upper airway muscle tone has been controversial and poorly reported. These investigators reviewed the evidence to evaluate the effectiveness of these methods. Data sources are from the Cochrane Library, Medline, Embase and Scielo, registries of ongoing trials, theses indexed at Biblioteca Regional de Medicina/Pan-American Health Organization of the World Health Organization and the reference lists of all the trials retrieved. This was a review of randomized or quasi-randomized double-blind trials on OSA. Two reviewers independently applied eligibility criteria. One reviewer assessed study quality and extracted data, and these processes were checked by a second reviewer. The primary outcome was a decrease in the AHI of below 5 episodes per hour. Other outcomes were subjective sleep quality, sleep quality measured by NPSG, quality of life measured subjectively and adverse events associated with the treatments. Three eligible trials were included -- 2 showed improvements through the objective and subjective analyses, and 1 showed improvement of snoring, but not of AHI while the subjective analyses showed no improvement. The adverse events were reported and they were not significant. The authors concluded that there is no accepted scientific evidence that methods aiming to increase muscle

tone of the stomatognathic system are effective in reducing AHI to below 5 events per hour. They stated that well-designed randomized controlled trials are needed to assess the effectiveness of such methods.

The European Respiratory Society's task force on non-CPAP therapies in sleep apneas (Randerath et al, 2011) summarized the effectiveness of alternative treatment options in OSAS. The task force evaluated the scientific literature according to the standards of evidence-based medicine. Evidence supports the use of mandibular advancement devices in mild-to-moderate OSAS. Maxillo-mandibular osteotomy seems to be as efficient as CPAP in patients who refuse conservative treatment. Distraction osteogenesis is usefully applied in congenital micrognathia or mid-face hypoplasia. There is a trend towards improvement after weight reduction. Positional therapy is clearly inferior to CPAP and long-term compliance is poor. Drugs, nasal dilators and apnea triggered muscle stimulation can not be recommended as effective treatments of OSAS at the moment. Although tongue muscle training improves snoring, it is not efficacious in the treatment of sleep apnoea in general. Nasal surgery, radiofrequency tonsil reduction, tongue base surgery, uvulo-palatal flap, laser mid-line glossectomy, tongue suspension and genioglossus advancement can not be recommended as single interventions. Uvulopalatopharyngoplasty, pillar implants and hyoid suspension should only be considered in selected patients and potential benefits should be weighed against the risk of long-term side-effects. Multi-level surgery is only a salvage procedure for OSA patients.

Percutaneous submental electrical stimulation during sleep has been suggested as a method for treating patients with OSA. Electrical stimulation to the submental region during OSA is reported to break the apnea without arousal and to diminish apneic index, time spent in apnea, and oxygen desaturation. The mode of breaking the apnea by electrical stimulation has not yet been shown. Moreover, genioglossus is supposed to be the muscle responsible for breaking the apnea by forward movement of the tongue. However, the therapeutic value of transcutaneous electrical stimulation of the genioglossus muscle in patients with OSA to reduce sleep-disordered breathing is still unclear. The European Respiratory Society's task force on non-CPAP therapies in sleep apneas (Randerath et al, 2011) noted that "[t]here are conflicting results on the clinical efficacy of apnoea triggered neurostimulation. Intraneuronal stimulation of the hypoglossus nerve and transcutaneous electrical stimulation of the genioglossus muscle showed significant

improvements of respiratory disturbances and sleep parameters without adverse effects. In contrast, other groups failed to find an enlargement of the upper airways by transcutaneous or intramuscular stimulation during wakefulness or sleep. However, undesirable contractions of the platysma or tongue were observed and arousals were induced".

Multiple Sleep Latency Test (MSLT)

The MSLT, most commonly used in the evaluation of narcolepsy, is also used to document daytime sleepiness in OSA. The MSLT evaluates the rapidity with which a patient falls asleep during daytime nap opportunities at 2-hour intervals throughout the day. The test is typically administered after an overnight polysomnogram. Similar to the polysomnogram, the EEG, EOG and EMG are routinely recorded. A sleep latency of less than 6 mins is considered clinically significant. Although the polysomnogram is always part of the work-up of OAS, the MSLT is considered expensive and time consuming and is infrequently performed. However, with the recent emphasis on excessive daytime sleepiness as an initial symptom of an obstructive sleep disorder, evaluating a patient's daytime sleepiness becomes more important, in order to distinguish true excessive daytime sleepiness from the occasional sleepiness that almost everyone experiences.

According to the Standards of Practice Committee of the American Academy of Sleep Medicine (Littner et al, 2005), the MSLT is indicated as part of the evaluation of patients with suspected narcolepsy and may be useful in the evaluation of patients with suspected idiopathic hypersomnia. The MSLT is not routinely indicated in the initial evaluation and diagnosis of OSAS, or in assessment of change following treatment with nasal CPAP. The MSLT is not routinely indicated for evaluation of sleepiness in medical and neurological disorders (other than narcolepsy), insomnia, or circadian rhythm disorders.

Assessment of Adequacy of Response to CPAP

In an article on the use of oral appliance therapy for OSA, Ferguson (2001) used a conservative definition of treatment success. A complete response is defined as a reduction in AHI to less than 5/hour. A partial response was defined as an improvement in symptoms combined with a greater than or equal to 50 % reduction in AHI but the AHI remained greater than 5/hour. Treatment

failures were defined as having ongoing symptoms and/or a less than 50 % reduction in AHI. By this definition, a reduction of 55 events/hour of sleep to 33 events/hour of sleep (40 % reduction in AHI) would not be considered as a good response to CPAP.

Wassmuth et al (2000) evaluated the ability of cautery-assisted palatal stiffening operation (CAPSO) to treat OSA syndrome. Twenty-five consecutive patients with OSA syndrome underwent CAPSO. Responders were defined as patients who had a reduction in AHI of 50 % or more and an AHI of 10 or less after surgery.

Furthermore, Heinzer et al (2001) noted that a good response to CPAP treatment is defined as an AHI of less than 10 events/hour.

Javaheri (2000) concluded that an AHI of 4 +/- 3 per hour signifies complete elimination of disordered breathing. The author prospectively studied 29 men with heart failure whose initial polysomnograms showed 15 or more episodes of apnea and hypopnea per hour (AHI). Twenty-one patients had predominately central and 8 patients OSA. All were treated with CPAP during the subsequent night. In 16 patients, CPAP resulted in virtual elimination of disordered breathing. In these patients, the mean AHI (36 +/- 12 [SD] versus 4 +/- 3 per hour, p = 0.0001), arousal index due to disordered breathing (16 +/- 9 versus 2 +/- 2 per hour, p = 0.0001), and percent of total sleep time below saturation of 90 % (20 +/- 23 % to 0.3 +/- 0.7 %, p = 0.0001) decreased, and lowest saturation (76 +/- 8 % versus 90 +/- 3 %, p = 0.0001) increased with CPAP. In 13 patients who did not respond to CPAP, these values did not change significantly. In patients whose sleep apnea responded to CPAP, the number of hourly episodes of nocturnal premature ventricular contractions (66 +/- 117 versus 18 +/- 20, p = 0.055) and couplets (3.2 +/- 6 versus 0.2 +/- 0.21, p = 0.031) decreased. In contrast, in patients whose sleep apnea did not respond to CPAP, ventricular arrhythmias did not change significantly. The author concluded that in 55 % of patients with heart failure and sleep apnea, first-night nasal CPAP eliminates disordered breathing and reduces ventricular irritability. Based on this study, an AHI of 4 +/- 3 per hour signifies complete elimination of disordered breathing.

The SleepStrip is an instrument used for screening of OSA. It incorporates signal detection, acquisition, as well as display in a disposable package. The device is placed on the upper lip at bed-time and adjusted until respiration is detected, as indicated by a flashing light. Two nasal thermistors and 1 oral thermistor produce flow signals that are processed within the SleepStrip's microprocessor. The 5 possible results are as follows: "0" (no apneas); "1" (mild sleep apnea, comparable to sleep laboratory AHI between 15 and 24); "2" (moderate sleep apnea, comparable to sleep laboratory AHI between 25 and 39); "3" (severe sleep apnea, comparable to sleep laboratory AHI of greater than 40); and "E" (error in measurement).

In a prospective, non-randomized double-blinded single cohort study, Pang et al (2006) examined the role of a portable screening device (SleepStrip) in the diagnosis of OSA. Patients with suspected OSA scheduled for an attended over-night Level I PSG and who consented to participate in the study wore the SleepStrip device at home the night after the PSG. The AHI determined by PSG was compared with the results of the SleepStrip recording. A total of 37 patients with a mean age of 52.1 +/- 12.2 years and mean body mass index of 35.7 +/- 5.2 participated in the study. The overall agreement between the AHI and the SleepStrip results using Cohen's Kappa value was 0.139 ($p = 0.19$). The sensitivity and specificity of the SleepStrip for diagnosing severe OSA when the AHI was greater than 40 were 33.3 % and 95 % ($p = 0.05$). When the AHI was greater than 25, the SleepStrip sensitivity and specificity were 43.8 % and 81.3 % ($p = 0.26$). The sensitivity and specificity of the SleepStrip for diagnosing OSA in patients with an AHI greater than 15 were 54.6 % and 70 %, respectively ($p = 0.26$). The authors concluded that SleepStrip has a low correlation with the AHI as measured by PSG; they stated that further studies are needed before this device can be recommended as a screening tool for the diagnosis of OSA.

In a prospective, non-randomized, double-blinded single cohort study, Ozmen et al (2011) examined the reliability of SleepStrip as a screening test in OSA syndrome. A total of 72 patients (50 males, 22 females; mean age of 51.4 +/- 11.1 years; range of 20 to 74 years) with OSA syndrome were included in this study between May 2008 and February 2009. Patients who underwent an attended over-night PSG and consented to participate in the study were asked to use SleepStrip device within the week following PSG recording. The AHI was compared with the SleepStrip score (Sscore). The mean BMI of patients was 31.1 +/- 4.3. Both AHI and Sscore

were obtained in 64 patients. There was a strong correlation between Sscore and AHI ($r = 0.76$, $p < 0.001$). The sensitivity and specificity of the SleepStrip were 94.4 % and 93.5 % when used to diagnose cases with AHI = or > 40. The sensitivity and specificity of the SleepStrip was reduced to 80 % and 87.2 % when AHI threshold was chosen as equal or greater than 25 and 83.3 % and 76. 5 % for AHI equal to or greater than 15, respectively. The authors concluded that there is a strong correlation between SleepStrip and AHI. SleepStrip was found to be effective in diagnosing severe OSAS with AHI equal or greater than 40, however, its diagnostic capability was reduced in patients with lower AHI's who constitute the main target of screening.

The Encore tongue base suspension received FDA 510(k) clearance and is intended to be used for anterior advancement of the tongue base by means of a bone screw threaded with suture. It is indicated for the treatment of mild or moderate OSA and/or snoring. However, there is currently insufficient evidence to support its use.

On behalf of the European Respiratory Society task force on non-CPAP therapies in sleep apnea, Randerath et al (2011) stated that "Evidence supports the use of mandibular advancement devices in mild-to-moderate OSAS. Maxillomandibular osteotomy seems to be as efficient as continuous positive airway pressure (CPAP) in patients who refuse conservative treatment. Distraction osteogenesis is usefully applied in congenital micrognathia or midface hypoplasia. There is a trend towards improvement after weight reduction. Positional therapy is clearly inferior to CPAP and long-term compliance is poor. Drugs, nasal dilators and apnoea triggered muscle stimulation cannot be recommended as effective treatments of OSAS at the moment. Nasal surgery, radiofrequency tonsil reduction, tongue base surgery, uvulopalatal flap, laser midline glossectomy, tongue suspension and genioglossus advancement cannot be recommended as single interventions. Uvulopalatopharyngoplasty, pillar implants and hyoid suspension should only be considered in selected patients and potential benefits should be weighed against the risk of long-term side-effects. Multilevel surgery is only a salvage procedure for OSA patients".

The Winx therapy system/oral pressure therapy (OPT) is a light, oral vacuum delivered by a quiet console through a slim tube connected to a soft, flexible mouth-piece. The mouthpiece and vacuum work together to gently pull the soft palate forward and stabilize the tongue, increasing the size of the airway and allowing for natural breathing to occur during sleep. Farid-Moayer et al

(2013) conducted a proof-of-concept study that suggested that OPT can produce clinically relevant relief of OSA in certain subjects who are readily identified by PSG during trial use of the noninvasive system. In this single-center, proof-of-concept, single-treatment-night study, subjects with OSA underwent a baseline PSG study followed by PSG during use of an OPT system. Fifty-four men and 17 women, aged 53.2 ± 11.5 years (mean \pm SD) had a baseline apnea-hypopnea index (AHI) greater than 5 events per hour. The authors reported that OPT was generally well tolerated with no serious adverse events. The authors found that OPT significantly decreased AHI from 34.4 ± 28.9 events per hour (mean \pm SD) at baseline to 20.7 ± 23.3 ($p < 0.001$). Treatment produced an AHI less than 10 in 48% of the subjects. The authors stated that OPT significantly improved oxygen desaturation index ($p < 0.001$) and increased the percentage of the night with oxygen saturation of 90% or greater ($p = 0.028$). Stage-N1 sleep shifts, total sleep-stage shifts, awakenings and the percentage of sleep time spent in N1 sleep were significantly reduced with treatment. Additional studies of longer duration and larger numbers of patients are necessary, as are studies comparing results of OPT with CPAP as current standard of care.

Colrain et al (2013) evaluated the impact of a novel non-invasive oral pressure therapy (OPT) (Winx®, ApniCure) system on polysomnographic measures of sleep-disordered breathing, sleep architecture, and sleep stability in OSA. A 4-week, multi-center, prospective, open-label, randomized, cross-over, first-night order of control versus treatment, single-arm trial was conducted in 5 AASM-accredited sleep clinics and 1 research laboratory. A total of 63 subjects (analysis cohort) were studied from a screening cohort of 367 subjects. The analysis cohort was 69.8 % men, ages 53.6 ± 8.9 years (mean \pm SD), BMI of $32.3 \pm 4.5\text{kg/m}^2$, with mild-to-severe OSA. At treatment initiation, subjects received random assignment to 1 night with and 1 without (control) treatment, and they were assessed again following 28 nights of treatment. Breathing and sleep architecture were assessed each night based on blind scoring by a single centralized scorer using AASM criteria. Average nightly usage across the take-home period was 6.0 ± 1.4 hrs. There were no severe or serious device-related adverse events (AEs). Median AHI was 27.5 events/hr on the control night, 13.4 events/hr on the first treatment night, and 14.8 events/hr after 28 days of treatment. A clinically significant response (treatment AHI less than or equal to 10/hr and less than or equal to 50 % of control values) was seen in 20 of the 63 subjects evaluated. Rapid eye movement percentage (REM %) was significantly increased, and N1 %, stage shifts to N1 sleep, overall stage shifts, total awakenings, and arousals/hr were all significantly reduced at

both treatment nights compared to controls. Mean ESS score was significantly reduced from 12.1 to 8.6 (Cohen d effect size, 0.68) in those untreated for 2 or more weeks prior to OPT study participation and remained unchanged in subjects who directly switched from CPAP therapy to OPT. The authors concluded that clinically significant improvements in sleep quality and continuity, AHI, oxygen desaturation index (ODI), ESS, and overall clinical status were achieved in an easily identified subgroup; OPT was safe and well-tolerated and nightly usage was high. They stated that these findings suggested that OPT may provide useful therapy for a subset of OSA patients who do not tolerate nasal CPAP.

This study had several drawbacks: (i) treatment efficacy was limited to 2 single-night studies, 1 at the beginning and the other at the end of a 28-day take-home period. Future studies will need to extend the period of use for both safety and long-term efficacy evaluation; (ii) the study should have had multiple measurement points, if not nightly monitoring of oxygen saturation in the home; (iii) the study was conducted on a highly selected study population; and (iv) the lack of a sham-placebo controlled condition. Furthermore, a review on “Alternative devices for obstructive sleep apnea” (Barone, 2013) states that “the initial data are impressive, and OPT certainly seems safe, but as with all new modalities, real-world experience needs to be ascertained and more extensive clinical trials need to be performed. The manufacturer reports that this promising new device should be widely available this year”. The potential benefits of diagnostic audio recording, used alone or in conjunction with pulse oximetry, has not been demonstrated to provide clinical benefits equivalent to the currently accepted standard of care, PSG. While such methods do potentially identify occurrences of sleep apnea, other aspects of physiological functioning are not recorded simultaneously, thus providing an incomplete clinical picture and allowing the possibility of misdiagnosis.

Dafna et al (2012) described a novel method for sleep quality analysis. Its purpose is to assist an alternative non-contact method for detecting and diagnosing sleep related disorders based on acoustic signal processing. In this study, audio signals of 145 patients with OSA were recorded (more than 1,000 hours) in a sleep laboratory and analyzed. The method is based on the assumption that during sleep the respiratory efforts are more periodically patterned and consistent relative to a waking state; furthermore, the sound intensity of those efforts is higher, making the pattern more noticeable relative to the background noise level. The system was trained on 50

subjects and validated on 95 subjects. The accuracy of the system for detecting sleep/wake state is 82.1 % (epoch by epoch), resulting in 3.9 % error (difference) in detecting sleep latency, 11.4 % error in estimating total sleep time, and 11.4 % error in estimating sleep efficiency. The clinical effectiveness of this novel system needs to be ascertained in well-designed studies.

Yadollahi et al (2013) stated that tracheal respiratory sound analysis is a simple and non-invasive way to study the pathophysiology of the upper airway and has recently been used for acoustic estimation of respiratory flow and sleep apnea diagnosis. However, in none of the previous studies was the respiratory flow-sound relationship studied in people with OSA, nor during sleep. In this study, these researchers recorded tracheal sound, respiratory flow, and head position from 8 non-OSA and 10 OSA individuals during sleep and wakefulness. They compared the flow-sound relationship and variations in model parameters from wakefulness to sleep within and between the 2 groups. The results showed that during both wakefulness and sleep, flow-sound relationship follows a power law but with different parameters. Furthermore, the variations in model parameters may be representative of the OSA pathology. The other objective of this study was to examine the accuracy of respiratory flow estimation algorithms during sleep: these researchers investigated 2 approaches for calibrating the model parameters using the known data recorded during either wakefulness or sleep. The results showed that the acoustical respiratory flow estimation parameters change from wakefulness to sleep. Therefore, if the model was calibrated using wakefulness data, although the estimated respiratory flow follows the relative variations of the real flow, the quantitative flow estimation error would be high during sleep. On the other hand, when the calibration parameters were extracted from tracheal sound and respiratory flow recordings during sleep, the respiratory flow estimation error is less than 10 %.

Murphy and associates (2015) determined the effect of glossectomy as part of multi-level sleep surgery on sleep-related outcomes in patients with OSA. Two independent researchers conducted the review using PubMed-NCBI and Scopus literature databases. Studies on glossectomy for OSA that reported pre- and post-operative AHI score with 10 or more patients were included. A total of 18 articles with 522 patients treated with 3 glossectomy techniques (midline glossectomy, lingualplasty, and submucosal minimally invasive lingual excision) met inclusion criteria. Pooled analyses (baseline versus post-surgery) showed a significant improvement in AHI (48.1 ± 22.01 to 19.05 ± 15.46 , $p < 0.0001$), Epworth Sleepiness Scale (ESS;

11.41 ± 4.38 to 5.66 ± 3.29 , $p < 0.0001$), snoring visual analog scale (VAS; 9.08 ± 1.21 to 3.14 ± 2.41 , $p < 0.0001$), and Lowest O₂ saturation (76.67 ± 10.58 to 84.09 ± 7.90 , $p < 0.0001$). Surgical success rate was 59.6 % (95 % confidence interval [CI]: 53.0 % to 65.9 %) and surgical cure was achieved in 22.5 % (95 % CI: 11.26 % to 36.26 %) of cases. Acute complications occurred in 16.4 % (79/481) of reported patients. Glossectomy was used as a standalone therapy in 24 patients.

In this limited cohort, significant reductions in AHI (41.84 ± 32.05 to 25.02 ± 20.43 , $p = 0.0354$) and ESS (12.35 ± 5.05 to 6.99 ± 3.84 , $p < 0.0001$) were likewise observed. The authors concluded that glossectomy significantly improved sleep outcomes as part of multi-level surgery in adult patients with OSA. They stated that currently, there is insufficient evidence to analyze the role of glossectomy as a stand-alone procedure for the treatment of sleep apnea, although the evidence suggests positive outcomes in select patients.

Furthermore, a review on “Alternative devices for obstructive sleep apnea” (Barone, 2013) states that “The future -- Next-generation respiratory-triggered implantable devices have recently been designed and have been engineered to provide intermittent electrical impulses to the hypoglossal nerve via an implanted cuff electrode. These devices monitor respiration, via implanted thoracic leads, by sensing changes in motion of the chest wall. Electrical stimulation to the hypoglossal nerve is then provided cyclically during inspiration (which represents the most vulnerable period with regard to upper airway narrowing and collapse). When stimulated, the hypoglossal nerve causes the genioglossus muscle to contract, which results in an anterior displacement of the base of the tongue and an enlargement of the upper airway. The hypoglossal branches that innervate the genioglossus contain mostly efferent fibers, with minimal afferent input; this allows for activation of the genioglossus with less possibility of arousal. In one study, there was a significant improvement from baseline to 6 months in AHI (43.1 ± 17.5 [severe] to 19.5 ± 16.7 [moderate]) and ESS (12.1 ± 4.7 [excessive sleepiness] to 8.1 ± 4.4 [borderline sleepiness]). Another recent study presented initial data suggesting that upper airway stimulation can be effective and safe in certain patients with moderate to severe OSA who are unable or unwilling to use CPAP. However, like all surgical treatments, this is subject to unpredictable results, potential for adverse events, and likely large expense; fortunately, it will be just one of several alternatives to CPAP available in the near future”.

In a prospective, non-randomized trial using historical controls, Lee et al (2012) evaluated the use of transoral robot-assisted lingual tonsillectomy and UPPP for the surgical management of tongue base obstruction in patients with OSA. Patients underwent drug-induced sleep endoscopy, transoral robot-assisted lingual tonsillectomy with UPPP, and pre-operative and post-operative PSG. A total of 20 patients have completed the study to date. The rate of surgical success was 45 %, and the rate of surgical response was 65 %. The mean pre-operative AHI of 55.6 decreased by 56.7 %, to a mean post-operative value of 24.1 ($p < 0.001$), and the minimum arterial oxygen saturation increased from the mean pre-operative value of 75.8 % to the mean post-operative value of 81.7 % ($p = 0.013$). The mean ESS score improved from 13.4 to 5.9 ($p = 0.003$). One patient had post-operative bleeding that required cauterization, resulting in a major complication rate of 4.2 %. The authors concluded that transoral robot-assisted lingual tonsillectomy with UPPP is a novel technique for the surgical management of OSA that results in a significant decrease in the AHI, a significant improvement in minimum arterial oxygen saturation, and a significant improvement in the ESS score and has an acceptable complication rate. The findings of this small, non-randomized study need to be validated by well-designed studies.

In a retrospective case-series review, Suh et al (2013) analyzed the overall success rate of open midline glossectomy with lingual tonsillectomy in the surgical management of OSAS as well as a subset analysis to determine whether certain patient factors influence clinical outcome. A total of 50 consecutive patients who had moderate to severe OSAS with Friedman tongue position III or IV and underwent midline glossectomy with lingual tonsillectomy as part of multi-level sleep apnea surgery and had pre- and post-surgery in-laboratory sleep studies performed. The overall success rate was 56.0 % using success defined as a post-operative AHI less than 20 and a decrease of greater than 50 %. Median AHI decreased from 52.0 to 18.3 with a median change of -26.1 (inter-quartile range, -41.6 and -17.1). Of significance on subset analysis, patients with a pre-operative AHI less than 60 had a 68.8 % success rate ($p = 0.02$), and patients with Friedman tongue position III had a 75.9 % success rate ($p = 0.0009$). The authors concluded that the findings of this case series would suggest that multi-level sleep apnea surgery, incorporating midline glossectomy with lingual tonsillectomy, is a valid alternative for managing moderate-to-

severe OSAS in patients who do not respond or are resistant to CPAP therapy. In patients with a pre-operative AHI less than 60 or Friedman tongue position III, surgical success rate is significantly improved.

Moreover, an UpToDate review on “Management of obstructive sleep apnea in adults” (Kryger, 2013) states that “Laser-assisted and radiofrequency ablation (RFA) are less invasive variants of UPPP. Other common surgical procedures for OSA include septoplasty, rhinoplasty, nasal turbinate reduction, nasal polypectomy, palatal advancement pharyngoplasty, tonsillectomy, adenoidectomy, palatal implants (i.e., Pillar procedure), tongue reduction (partial glossectomy, lingual tonsillectomy), genioglossus advancement, and maxillomandibular advancement. A systematic review reported that most of the evidence related to such surgical treatments is from case series. Meta-analyses of data extracted from these series suggest that UPPP, laser-assisted uvulopalatoplasty, radiofrequency ablation, and maxillomandibular advancement (MMA) decrease the AHI. MMA is most consistently associated with a decreased AHI, although the morbidity of MMA has not been determined. These meta-analyses were limited by a serious risk for bias and inconsistency among the series Only a small number of trials have directly compared surgery to either conservative management or a nonsurgical therapy. Overall, the trials have failed to consistently demonstrate a benefit from surgical therapy. While this could be a true effect, it may also reflect the small sample sizes, the heterogeneous patient populations, or the use of short-term outcome measures”.

Expansion sphincteroplasty is a modification of UPPP; it removes the remaining tonsil, creates an incision on the soft palate, pulls the muscles of the back wall of the tonsils forward to increase throat space and pulls stitches to further open the space. This surgery preserves the uvula most of the time.

Pensler and Reich (1991) compared speech results after the pharyngeal flap and the dynamic sphincteroplasty procedures. Eighty-five patients underwent surgery to reduce velopharyngeal incompetence with either a pharyngeal flap ($n = 75$) or a dynamic sphincteroplasty ($n = 10$) performed between April 1958 and August 1989, and were evaluated pre-operatively and post-operatively by a plastic surgeon, speech pathologist, and otolaryngologist. Improvement in speech was noted in 75 % ($n = 56$) of the patients with pharyngeal flaps and 70 % ($n = 7$) of the

patients with dynamic sphincteroplasties post-operatively; 30 % of the patients in both groups showed no improvement post-operatively in speech; 3 patients (4 %) who underwent pharyngeal flap procedures developed sleep apnea post-operatively. The authors concluded that persistent velopharyngeal incompetence may be treated effectively with either a pharyngeal flap or a dynamic sphincteroplasty. Either procedure appeared to result in improved speech in most patients.

Pang and Woodson (2006) stated that the lateral pharyngeal wall has been known to contribute to the collapse of the upper airway in many patients with obstructive sleep apnea (OSA). It is difficult to create enough tension in the lateral pharyngeal walls to prevent its collapse. To the authors' knowledge, there has not been any surgery that specifically addresses this issue. The lateral pharyngoplasty described by Cahali aims to address the lateral pharyngeal wall collapse in patients with OSA. However, post-operatively, many patients had prolonged dysphagia. The expansion sphincter pharyngoplasty is a simple technique that stiffens the lateral pharyngeal walls and prevents its collapse in patients with OSA. The technique basically consists of a tonsillectomy, expansion pharyngoplasty, rotation of the palatopharyngeus muscle, a partial uvulectomy, and closure of the anterior and posterior tonsillar pillars. This procedure can be performed alone or as part of the multilevel surgical algorithm in the treatment of OSA. Moreover, the authors noted that "This new technique of expansion sphincter pharyngoplasty may offer benefits over traditional methods of UPPP in patients with OSA with small tonsils, Friedman stage II and III, and lateral wall collapse noted on endoscopic examination. The procedure has promising results, is anatomically sound, and has minimal complications".

Mann et al (2011) noted that velopharyngeal dysfunction has been treated with either a pharyngeal flap or sphincteroplasty with varying degrees of success. Both of these entities have their own series of problems, with sleep apnea and nasal mucous flow disruptions at the forefront. The purpose of this study was to review the senior author's (R.J.M.) experience performing the double-opposing buccal flap for palatal lengthening. All patients who were treated with double-opposing buccal flaps between October of 1994 and July of 2007 were reviewed. These patients presented with varying degrees of velopharyngeal dysfunction showing some degree of velar movement at the time of surgery. Pre-operative and post-operative speech results were reviewed for comparison. A total of 27 patients underwent palatal lengthening, with

an average length of follow-up of 58 months. Distal flap necrosis occurred in 2 patients. The level of intelligibility (65.4 % versus 95.5 %) and resonance (moderately hyper-nasal versus normal resonance) improved significantly postoperatively ($p < 0.0001$). Only 1 patient required the addition of a pharyngeal flap for persistent velopharyngeal dysfunction, and there were no post-operative issues with sleep apnea. The authors concluded that the double-opposing buccal flap is an effective technique for lengthening the palate, improving speech, and decreasing the risks of post-operative sleep apnea. All patients experienced a dramatic improvement in their resonance and intelligibility. They stated that this technique appeared most effective in patients with intact velar movement who demonstrate a small-to-moderate posterior velar gap. The double-opposing buccal flap is a useful means of treating velopharyngeal dysfunction, thus serving as an adjunct when improving pharyngeal closure.

Also, and UpToDate review on “Overview of obstructive sleep apnea in adults” (Strohl, 2014) does not mention sphincteroplasty as a management option.

Kitamura et al (2014) evaluated the objective and subjective improvement after multi-level surgery, genioglossus advancement (GA) plus UPPP for the treatment of OSAS. Genioglossus advancement and UPPP were undertaken in 24 patients with moderate and severe OSAS between January 2006 and December 2011. Epworth Sleepiness Scale score, snoring, the feeling of having slept well and PSG were used for the evaluation of surgical outcomes. In addition, these researchers determined whether baseline PSG, cephalometry, and anthropometry data could predict GA and UPPP success or failure. The mean ESS score decreased significantly from 12.96 to 7.08. The mean AHI improved from 37.3 to 19.33. Objective success as evaluated by a 50 % reduction in AHI or by AHI less than 15 was obtained in 16 of 24 patients. The lowest oxygen saturation and stage 1 and stage 2 were also improved significantly. There were no major post-operative complications. There were significant differences in SNA, SNB, FX and PNS-P (length of soft palate) between the success and failure of GA and UPPP. The indication of GA and UPPP were SNA greater than 79.11 degrees, SNB greater than 75.69 degrees, FX greater than 78.67 degrees, and $36.79 \text{ mm} < \text{PNS-P} < 42.29 \text{ mm}$. The authors concluded that GA and UPPP surgeries are effective and safe for patients with moderate and severe OSAS. However, they stated that further studies are needed to decide definitively if GA and UPPP are appropriate treatments for OSAS.

Hypoglossal Nerve Stimulation

Eisele et al (1997) examined the motor responses resulting from direct electrical stimulation of the hypoglossal (HG) nerve and correlated these responses to changes in upper airway patency during sleep. The motor effects of direct electrical stimulation of the main trunk of the HG nerve and the branch that supplies the genioglossus muscle during anesthesia and wakefulness were assessed visually. Responses in airflow during sleep to HG nerve stimulation were assessed with standard polysomnographic techniques. A total of 15 patients undergoing a surgical procedure that involved the neck that exposed the HG nerve and 5 volunteer patients with OSA constituted the study population. The main trunk ($n = 3$) and genioglossus branch ($n = 2$) of the HG nerve were stimulated electrically with a half-cuff tri-polar electrode. Stimulation of the branch of the HG nerve that innervates the genioglossus muscle caused protrusion and contralateral deviation of the tongue. Stimulation of the main trunk of the HG nerve caused slight ipsilateral deviation and retrusion of the tongue. The arousal threshold for stimulation exceeded the motor recruitment threshold by $0.8 +/ - 0.4$ V. Inspiratory airflow increased in all patients by $184.5 +/ - 61.7$ ml/s (mean $+/-$ SD; $p = 0.02$, analysis of variance) with stimulation. The authors concluded that direct HG nerve stimulation below the arousal threshold can improve airflow in patients with OSA. The findings of this small study need to be validated by well-designed studies with larger sample size and follow-ups. Eisele et al (2003) noted that the feasibility and potential of upper airway stimulation for the treatment of OSA have been demonstrated. Moreover, they stated that further studies and stimulation-system refinements are presently underway, with hopes of establishing upper airway stimulation as a therapeutic option for this challenging disorder.

Kezirian et al (2010) noted that upper airway occlusion in OSA has been attributed to a decline in pharyngeal neuromuscular activity occurring in a structurally narrowed airway. Surgical treatment focuses on the correction of anatomic abnormalities, but there is a potential role for activation of the upper airway musculature, especially with stimulation of the HG nerve and genioglossus muscle. These investigators presented evidence from research on upper airway neuromuscular electrical stimulation in animals and humans. They also presented results from 8 OSA patients with a fully implanted system for HG nerve stimulation, demonstrating an improvement in upper airway collapsibility and OSA severity. Moreover, they stated that future research, including

optimization of device features and stimulation parameters as well as patient selection, is necessary to make HG nerve stimulation a viable alternative to positive airway pressure therapy and upper airway surgical procedures.

Oliven (2011) reviewed a new treatment modality, HG stimulation, recently evaluated by multiple physiological studies and currently assessed by several clinical studies. A phase I, implantable HG nerve stimulation multi-center study was published in 2001. Significant reduction in AHI was reported in 7 of the 8 implanted OSA patients, but technical faults precluded prolonged follow-up. Over the past 2 years, 3 new HG nerve stimulation systems have been evaluated in more than 60 OSA patients. In adequately selected patients, a more than 50 % reduction in AHI was observed. Usually, a decrease in OSA severity from moderate-severe to mild-minimal can be achieved. The author concluded that ongoing research, including recent initiation of a large multi-center phase III study, suggested that HG nerve stimulators are likely to be available as a new treatment modality within a few years. Moreover, they stated that additional data are needed to define which OSA patients are most likely to benefit from HG nerve stimulation. Continuous refinement of electrodes design is likely to improve stimulation efficacy in coming years.

In 2 consecutive open prospective studies, Van de Heyning et al (2012) examined the safety and preliminary effectiveness of the Upper Airway Stimulation (UAS) system, and identified baseline predictors for therapy success. The UAS systems were implanted in patients with moderate-to-severe OSA who failed or were intolerant of CPAP. The study was conducted in 2 parts. In part 1, patients were enrolled with broad selection criteria; AHI was collected using laboratory-based PSG at pre-implant and post-implant visits. Epworth Sleepiness Scale and Functional Outcomes of Sleep Questionnaire (FOSQ) were also collected. In part 2, patients were enrolled using selection criteria derived from the experience in part 1. In part 1, 20 of 22 enrolled patients (2 exited the study) were examined for factors predictive of therapy response. Responders had both a BMI of less than or equal to 32 and AHI less than or equal to 50 ($p < 0.05$) and did not have complete concentric palatal collapse. Part 2 patients ($n = 8$) were selected using responder criteria and showed an improvement on AHI from baseline, from 38.9 ± 9.8 to 10.0 ± 11.0 ($p < 0.01$) at 6 months post-implant. Both ESS and FOSQ improved significantly in part 1 and 2 subjects. The authors concluded that the current study has demonstrated that therapy with upper

airway stimulation is safe and effective in a select group of patients with moderate-to-severe OSA who cannot or will not use CPAP as primary treatment. These preliminary findings need to be validated by well-designed studies with larger sample size and longer follow-up.

Mwenge et al (2013) stated that CPAP is an effective but cumbersome treatment for OSA. Non-compliant patients need alternative therapies. These researchers studied a tongue neurostimulation approach: targeted hypoglossal neurostimulation (THN) therapy with the aura6000™ System. A multi-contact electrode positioned around the main trunk of the 12th nerve connected to an implanted pulse generator stimulates segments of the nerve, activating dilator muscles. The primary objective was to improve the polysomnographically determined AHI at 3 months, and maintain the improvement after 12 months of treatment. Overall, 13 out of 14 operated patients were successfully implanted. At 12 months, the AHI decreased from 45 ± 18 to 21 ± 17 , a 53 % reduction ($p < 0.001$). The 4 % oxygen desaturation index fell from 29 ± 20 to 15 ± 16 and the arousal index from 37 ± 13 to 25 ± 14 , both $p < 0.001$. The ESS score decreased from 11 ± 7 to 8 ± 4 ($p = 0.09$). Targeted hypoglossal neurostimulation was neither painful nor awakened patients, who all complied with therapy. Transient tongue paresis occurred in 2 subjects. The authors concluded that the present study represented the longest study of any HG nerve neurostimulation reported to date. They stated that THN is safe and effective to treat OSA in patients not compliant with CPAP. The findings of this small study need to be validated by well-designed studies.

The American Academy of Sleep Medicine's review on "Obstructive sleep apnea" (2008) did not mention the use of HG nerve stimulation as a therapeutic option. An UpToDate review on "Management of obstructive sleep apnea in adults" (Kryger, 2013) does not mention the use of HG nerve stimulation as a therapeutic option.

Strollo et al (2014) evaluated the safety and effectiveness of upper-airway stimulation at 12 months for the treatment of moderate-to-severe OSA. Using a multi-center, prospective, single-group, cohort design, these researchers surgically implanted an upper-airway stimulation device in patients with OSA who had difficulty either accepting or adhering to CPAP therapy. The primary outcome measures were the AHI (with a score of greater than or equal to 15 indicating moderate-to-severe apnea) and the ODI (the number of times per hour of sleep that the blood oxygen level

drops by greater than or equal to 4 percentage points from baseline). Secondary outcome measures were the ESS, the FOSQ, and the percentage of sleep time with the oxygen saturation less than 90 %. Consecutive participants with a response were included in a randomized, controlled therapy-withdrawal trial. The study included 126 participants; 83 % were men. The mean age was 54.5 years, and the mean BMI was 28.4. The median AHI score at 12 months decreased 68 %, from 29.3 events/hour to 9.0 events/hour ($p < 0.001$); the ODI score decreased 70 %, from 25.4 events/hour to 7.4 events/hour ($p < 0.001$). Secondary outcome measures showed a reduction in the effects of sleep apnea and improved quality of life. In the randomized phase, the mean AHI score did not differ significantly from the 12-month score in the non-randomized phase among the 23 participants in the therapy-maintenance group (8.9 and 7.2 events/hour, respectively); the AHI score was significantly higher (indicating more severe apnea) among the 23 participants in the therapy-withdrawal group (25.8 versus 7.6 events/hour, $p < 0.001$). The ODI results followed a similar pattern. The rate of procedure-related serious adverse events was less than 2 %. The authors concluded that in this uncontrolled cohort study, upper-airway stimulation led to significant improvements in objective and subjective measurements of the severity of OSA. Moreover, they stated that “Additional objective data on adherence will be required to confirm the findings of the current study”. Exclusion criteria included BMI more than 32, neuromuscular disease, hypoglossal-nerve palsy, severe restrictive or obstructive pulmonary disease, moderate-to-severe pulmonary hypertension, severe valvular heart disease, NYHA class III or IV heart failure, recent myocardial infarction, severe cardiac arrhythmias within past 6 months, persistent HTN despite medication use, active psychiatric disease, and coexisting nonrespiratory sleep disorders. Limitations included no concurrent control group. The participants served as their own control.

Strollo et al. (2015) conducted a prospective, multicenter, single-group cohort study (STAR trial) to determine the stability of improvement in polysomnographic measures of sleep disordered breathing, patient reported outcomes, the durability of hypoglossal nerve recruitment and safety at 18 months. The study consisted of 126 adults with average BMI of 28.4 (range 18.4-32.5). Primary outcome measures were the AHI and the 4% ODI. Secondary outcome measures were the Epworth Sleepiness Scale (ESS), the Functional Outcomes of Sleep Questionnaire (FOSQ), and oxygen saturation percent time < 90% during sleep. Stimulation level for each participant was collected at three predefined thresholds during awake testing. The primary outcomes measures

(AHI and ODI) were improved at both 12 and 18 months compared to baseline. The median AHI was reduced by 67.4% from the baseline of 29.3/h to 9.7/h at 18 mo. The median ODI was reduced by 67.5% from 25.4 to 8.6/h at 18 mo. Response to therapy defined as, at least a 50% reduction and AHI < 20/h, was achieved in 64% of participants at 18 months using intent-to-treat analysis. There were 29%, 52%, and 69% of participants with AHI less than 5, 10, or 15 at 18, respectively. The FOSQ and ESS improved significantly at 18 mo compared to baseline values. The functional threshold was unchanged from baseline at 18 mo. Two participants experienced a serious device-related adverse event requiring neurostimulator repositioning and fixation. No tongue weakness reported at 18 mo. The authors concluded that UAS via the hypoglossal nerve maintained a durable effect of improving airway stability during sleep and improved patient reported outcomes without an increase of the stimulation thresholds or tongue injury at 18 months of follow-up.

Certal et al (2015) systematically reviewed the evidence regarding the safety and effectiveness of hypoglossal nerve stimulation (HNS) as an alternative therapy in the treatment of obstructive sleep apnea (OSA). Scopus, PubMed, and Cochrane Library databases were searched (updated through September 5, 2014). Studies were included that evaluated the effectiveness of HNS to treat OSA in adults with outcomes for apnea-hypopnea index (AHI), oxygen desaturation index (ODI), and effect on daytime sleepiness (Epworth Sleepiness Scale [ESS]). Tests for heterogeneity and subgroup analysis were performed. A total of 6 prospective studies with 200 patients were included in this review. At 12 months, the pooled fixed effects analysis demonstrated statistically significant reductions in AHI, ODI, and ESS mean difference of -17.51 (95 % CI: -20.69 to -14.34); -13.73 (95 % CI: -16.87 to -10.58), and -4.42 (95 % CI: -5.39 to -3.44), respectively. Similar significant reductions were observed at 3 and 6 months. Overall, the AHI was reduced between 50 % and 57 %, and the ODI was reduced between 48 % and 52 %. Despite using different hypoglossal nerve stimulators in each subgroup analysis, no significant heterogeneity was found in any of the comparisons, suggesting equivalent efficacy regardless of the system in use. The authors concluded that the findings of this review revealed that HNS therapy may be considered in selected patients with OSA who fail medical treatment. Moreover, they stated that further studies comparing HNS with conventional therapies are needed to definitively evaluate outcomes.

Mwenge et al (2015) noted that OSA is a very frequent affliction that affects about 1 to 5 % of the adult population in its severe form. Continuous positive airway pressure is the most commonly used treatment and is highly effective, but its use is limited by low long-term adherence rates and overall poor acceptance among the patients. Therefore, there is a need for developing alternative approaches to OSA treatment, including a more “natural” concept of maintaining an open airway through neuromodulation. These investigators reviewed the concept, scientific rationale, and technical details of hypoglossal nerve stimulation. They also reviewed results of published clinical studies with several hypoglossal stimulation devices that are being investigated today. The authors stated that hypoglossal nerve stimulation appears to be a very promising treatment for patients with moderate-to-severe OSA. If its effectiveness is confirmed, it will probably be complementary with CPAP therapy and initially aimed at patients unable or unwilling to use CPAP. Once it becomes a standard therapy, its advantages might prove sufficient to challenge CPAP as the first-line therapy.

An UpToDate review on “Management of obstructive sleep apnea in adults” (Kryger and Malhotra, 2015) states that “Hypoglossal nerve stimulation via an implantable neurostimulator device is a novel treatment strategy that may have a role in selected patients with moderate to severe OSA who decline or fail to adhere to positive airway pressure therapy, but further data are required”.

In a randomized controlled therapy withdrawal study, Woodson et al (2014) evaluated the effectiveness and durability of UAS via the hypoglossal nerve on OSA severity including objective and subjective clinical outcome measures. A consecutive cohort of 46 responders at 12 months from a prospective phase III trial of 126 implanted participants were included in this report. Participants were randomized to either therapy maintenance (“ON”) group or therapy withdrawal (“OFF”) group for a minimum of 1 week. Short-term withdrawal effect as well as durability at 18 months of primary (AHI and oxygen desaturation index) and secondary outcomes (arousal index, oxygen desaturation metrics, ESS, FOSQ, snoring, and blood pressure) were assessed. Both therapy withdrawal group and maintenance group demonstrated significant improvements in outcomes at 12 months compared to study baseline. In the randomized assessment, therapy withdrawal group returned to baseline, and therapy maintenance group demonstrated no change. At 18 months with therapy on in both groups, all objective respiratory and subjective outcome measures showed sustained improvement similar to those observed at 12 months. The authors

concluded that withdrawal of therapeutic UAS resulted in worsening of both objective and subjective measures of sleep and breathing, which when resumed results in sustained effect at 18 months. They stated that reduction of OSA severity and improvement of quality of life were attributed directly to the effects of the electrical stimulation of the hypoglossal nerve. It should be noted that this was an industry-supported study.

In a multi-center, prospective cohort study, Woodson et al (2016) described the 36-month clinical and PSG outcomes in an OSA cohort treated with hypoglossal cranial nerve UAS. Subjects were participants (n = 116) at 36 months from a cohort of 126 implanted participants. Participants were enrolled in a prospective phase III trial evaluating the effectiveness of UAS for moderated to severe OSA. Prospective outcomes included AHI, oxygen desaturation index, other PSG measures, self-reported measures of sleepiness, sleep-related quality of life, and snoring. Of 126 enrolled participants, 116 (92 %) completed 36-month follow-up evaluation per protocol; 98 participants additionally agreed to a voluntary 36-month PSG. Self-report daily device usage was 81 %. In the PSG group, 74 % met the a priori definition of success with the primary outcomes of AHI, reduced from the median value of 28.2 events/hour at baseline to 8.7 and 6.2 at 12 and 36 months, respectively. Similarly, self-reported outcomes improved from baseline to 12 months and were maintained at 36 months. Soft or no snoring reported by bed partner increased from 17 % at baseline to 80 % at 36 months. Serious device-related AEs were rare, with 1 elective device explantation from 12 to 36 months. The authors concluded that long-term 3-year improvements in objective respiratory and subjective quality-of-life outcome measures were maintained; AEs were uncommon. They stated that UAS was a successful and appropriate long-term treatment for individuals with moderate-to-severe OSA. This was an industry-supported study.

In a prospective, multi-center, cohort study, Soose et al (2016) evaluated the long-term (24-month) effect of cranial nerve UAS therapy on patient-centered OSA outcome measures. A total of 126 patients with moderate-to-severe OSA who had difficulty adhering to positive pressure therapy and received the surgically implanted UAS system were included in this report.

Outcomes were measured at baseline and post-operatively at 12 months and 24 months, and included self-report and bed partner-report of snoring intensity, ESS, and FOSQ. Additional analysis included FOSQ subscales, FOSQ-10, and treatment effect size. Significant improvement in mean FOSQ score was observed from baseline (14.3) to 12 months (17.3), and the effect was

maintained at 24 months (17.2). Similar improvements and maintenance of effect were seen with all FOSQ subscales and FOSQ-10. Subjective daytime sleepiness, as measured by mean ESS, improved significantly from baseline (11.6) to 12 months (7.0) and 24 months (7.1). Self-reported snoring severity showed increased percentage of "no" or "soft" snoring from 22 % at baseline to 88 % at 12 months and 91 % at 24 months; UAS demonstrated large effect size (> 0.8) at 12 and 24 months for overall ESS and FOSQ measures, and the effect size compared favorably to previously published effect size with other sleep apnea treatments. The authors concluded that in a selected group of patients with moderate-to-severe OSA and BMI less than or equal to 32 kg/m², hypoglossal cranial nerve stimulation therapy can provide significant improvement in important sleep related quality-of-life outcome measures and the effect is maintained across a 2-year follow-up period.

The authors stated that the drawbacks of this study included the lack of a control group and the highly selected patient population based on clinical, polysomnographic, and endoscopic/anatomical screening criteria, which may limit generalizability of these findings to other OSA populations. This may also have introduced the possibility that a placebo effect could have contributed, at least in part, to the study findings. They noted that to corroborate these improvements in quality-of-life measures, long-term sleep laboratory data and other objective outcome measures, in conjunction with responder versus non-responder analysis, are needed to further demonstrate therapy effectiveness across a longitudinal care model.

Heiser and associates (2017) obtained additional safety and effectiveness data on the use of selective UAS during daily clinical routine. This was a multi-center, prospective, single-arm study under a common implant; and follow-up protocol took place in 3 German centers. Every patient who received an implant of selective upper airway stimulation was included in this trial (AHI greater than or equal to 15/hour and less than or equal to 65/hour and BMI less than 35 kg/m²).

Before and 6 months after surgery, a 2-night home sleep test was performed. Data regarding the safety and effectiveness were collected. From July 2014 through October 2015, a total of 60 patients were included. Every subject reported improvement in sleep and daytime symptoms.

The average usage time of the system was 42.9 ± 11.9 hours/week. The median AHI was

significantly reduced at 6 months from 28.6/hour to 8.3/hour. No patient required surgical revision of the implanted system. The authors concluded that selective UAS is a safe and effective therapy for patients with OSA and represents an option for its surgical treatment.

The authors noted that additional adherence data are needed for longer follow-up duration. They also stated that this current study cohort included patients who previously could not adhere to CPAP. The improved adherence with UAS was suggestive of its clinical utility for longitudinal patient management for OSA symptoms and risks from OSA-related comorbidities, meriting further prospective study. They stated that overall, surgical treatment with a fully implanted electrotherapeutic device system for selective UAS appeared to be a safe procedure in the clinical setting. This industry-supported study did not include a comparison group.

Afonso Delgado et al (2016) stated that OSAHS is a common disorder that has been identified as a contributor to cardiovascular disease making it a major public health problem; CPAP is the standard treatment but compliance is suboptimal. Mandibular advancement devices and surgery have limited indications, inconstant efficiency and potential irreversible side effects. Stimulation of the hypoglossal nerve, that innervates the genioglossus is now a new therapeutic option for moderate and severe cases of OSAHS. Two types of stimulation are currently available: (i) stimulation synchronous with inspiration and (ii) continuous stimulation. The authors concluded that indication of each type of stimulation and long-term effects still need to be assessed but the implantable nerve stimulation is a promising treatment for patients without a therapy solution so far. In a multi-center, prospective, cohort study, Gillespie et al (2017) evaluated patient-based outcomes of subjects in a large cohort study (the STAR trial [Stimulation Therapy for Apnea Reduction]) 48 months after implantation with an upper airway stimulation (UAS) system for moderate-to-severe OSA. Patients (n = 91) at 48 months from a cohort of 126 implanted participants were included in this analysis. A total of 126 subjects received an implanted UAS system in a prospective phase III clinical trial. Patient-reported outcomes at 48 months, including Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), and snoring level, were compared with pre-implantation baseline. A total of 91 subjects completed the 48-month visit. Daytime sleepiness as measured by ESS was significantly reduced ($p = 0.01$), and sleep-related quality of life (QOL) as measured by FOSQ significantly improved ($p = 0.01$) when compared with baseline. Soft to no snoring was reported by 85 % of

bed partners; 2 patients needed additional surgery without complication for lead malfunction. The authors concluded that UAS maintained a sustained benefit on patient-reported outcomes (ESS, FOSQ, snoring) at 48 months in select patients with moderate-to-severe OSA.

The authors stated that the main drawback of this study was the increased number of patients lost to follow-up at 48 months compared with 36 months (25 versus 4). Factors that influence adherence to follow-up include individual patient characteristics, social support, medical staff characteristics, and research study design. The trend of older age for those who completed follow-up versus those lost at 48 months was consistent with other trials that have noted poorer follow-up in younger cohorts, perhaps due to increased demands of work-life balance among younger subjects. With regard to medical staff, loss of a principal investigator and study site support accounted for 20 % of follow-up loss at 48 months. This trial, like many other multi-year trials, experienced greater loss of follow-up after 3 years. They noted that ongoing follow-up is needed to determine the natural product life of the device components.

In a prospective, multi-center, single-arm study, Steffen et al (2018) reported objective and patient-reported outcome after 12 months of implantation. Consecutive patients who received the upper airway stimulation (UAS) system (Inspire Medical Systems, Inc., Minneapolis, MN) were enrolled in 3 German centers. Key study exclusion criteria included body mass index (BMI) greater than 35 kg/m², apnea-hypopnea index (AHI) less than 15 or greater than 65, or complete concentric collapse at the soft palate during sedated endoscopy. Data collection at 6- and 12-month visit include home sleep test and patient-reported outcome measures. Among the total of 60 participants, the median AHI reduced from 28.6 to 9.5 from baseline to 12 months. Patient-reported outcome measured in Epworth Sleepiness Scale and Functional Outcomes of Sleep Questionnaire both improved significantly from baseline to 12 months. The average usage time was 39.1 ± 14.9 hours per week among all participants based on recordings by the implanted device; 1 patient requested a removal of the device for cosmetic and other personal reasons and was completed without sequelae. The authors concluded that the findings of this study supported that upper airway stimulation is a safe and effective therapeutic option for patients with OSA in routine clinical practice. Level of Evidence = 4. (This was an uncontrolled study with relatively small study with short-term follow-up)

Furthermore, an UpToDate review on “Management of obstructive sleep apnea in adults” (Kryger and Malhotra, 2017) states that “Hypoglossal nerve stimulation is a novel strategy that is emerging as a potential treatment option in selected patients ... Hypoglossal nerve stimulation via an implantable neurostimulator device is a novel treatment strategy that may have a role in selected patients with moderate to severe OSA, although early results are mixed and further data are needed”.

Hofauer et al. (2017) conducted a prospective cohort study to compare changes in sleep architecture during the diagnostic polysomnography and the post-implantation polysomnography in UAS in patients with OSA. The authors state that selective upper-airway stimulation (UAS) is a novel therapy for patients with obstructive sleep apnea (OSA). The study included 26 patients who received a UAS device (Inspire Medical Systems). Treatment outcome was evaluated 2 and 3 months after surgery. Data collection included demographics, body mass index (BMI), apnea hypopnea index (AHI), oxygen saturation and desaturation index (ODI), Epworth sleepiness score (ESS), arousal parameter, and sleep patterns. The mean age was 60.2 years, 25 patients were male, 1 patient was female. Mean BMI was 29.0 kg/m². The mean pre-implantation AHI of 33.9/h could be reduced to 9.1/h at 2 months post-implantation ($p < 0.001$). The amount of time spent in N1-sleep could be reduced from 23.2% at baseline to 16.0% at month 3 post-implantation. The amount of time spent in N2- and N3-sleep did not change during the observation period. A significant increase of the amount of REM sleep at month 2 (15.7%) compared to baseline (9.5%; $p = 0.010$) could be observed. A reduction of the number of arousals and the arousal index could be observed. The authors concluded that significant changes in sleep architecture of patients with OSA and sufficient treatment with UAS could be observed. A reduction of the amount of time spent in N1-sleep could be caused by treatment with UAS and the rebound of REM sleep, observed for the first time in a study on UAS, is also a potential marker of the efficacy of UAS on sleep architecture. Huntley et al. (2017) conducted a retrospective study to compare upper airway stimulation for the treatment of OSA at two academic centers between May 2014 and August 2016. The investigators recorded demographic data, Epworth Sleepiness Scale (ESS), and preoperative and postoperative polysomnographic information. They compared outcome data between institutions and subsequently combined the cohorts and compared baseline to posttreatment results. Cohort 1 consisted of 30 males and 18 females with mean BMI of 29.3. The mean preoperative apnea-hypopnea index (AHI), O₂ nadir, and ESS were 35.88, 80.96, and 11.09, respectively. The mean postoperative AHI, O₂ nadir, and ESS were 6.34, 88.04, and 5.77,

respectively. Cohort 2 consisted of 30 males and 19 females with a mean BMI of 27.7. The mean preoperative AHI, O₂ nadir, and ESS were 35.29, 79.58, and 10.94, respectively. The mean postoperative AHI, O₂ nadir, and ESS were 6.28, 84.35, and 6.60, respectively. The investigators found no difference in patients reaching a postoperative AHI less than 15, 10, and 5 when comparing the cohorts. After combining cohorts, they found a significant improvement in postoperative AHI, O₂ nadir, and ESS compared to preoperative values. Huntley and colleagues concluded that UAS appears to provide a viable alternative to continuous positive airway pressure, producing improvement in both polysomnographic and quality-of-life measures. Results are reproducible at high-volume centers. The position statement from the American Academy of Otolaryngology (AAO) (2016) states that the AAO “considers upper airway stimulation (UAS) via the hypoglossal nerve for the treatment of adult obstructive sleep apnea syndrome to be an effective second-line treatment of moderate to severe obstructive sleep apnea in patients who are intolerant or unable to achieve benefit with positive pressure therapy (PAP). Not all adult patients are candidates for UAS therapy and appropriate polysomnographic, age, BMI and objective upper airway evaluation measures are required for proper patient selection.” The Inspire Upper Airway Stimulation (UAS) (Inspire Medical Systems, Inc.) is an FDA-approved implanted upper airway stimulator that includes an implantable pulse generator and leads system, and external programmer indicated for second-line treatment of adult patients with moderate to severe obstructive sleep apnea (OSA). The system delivers mild stimulation to the hypoglossal nerve which controls the movement of the tongue and other key airway muscles. By stimulating these muscles, the airway remains open during sleep. The FDA eligibility criteria for the UAS implantation include age 22 years of age and older, moderate or severe OSA (defined as AHI 20 to 65 events/hour), predominantly obstructive events (defined as central and mixed apneas less than 25 percent of the total AHI), CPAP failure (defined as AHI >20 on CPAP) or intolerance (defined as use <4 hours per night, five nights per week; or unwillingness to use), no complete concentric velopharyngeal collapse on screening sleep endoscopy, and no other anatomical findings that would compromise performance of the device (eg, tonsil size 3 or 4). It is not recommended for patients with BMI >32 kg/m² (FDA, 2014; Inspire Medical Systems, 2014; Weaver and Kapur, 2017). Patients who are pregnant or plan to become pregnant, are unable or do not have the necessary assistance to operate the sleep remote, will require MRI (excluding Inspire 3028 system which has MRI labeling), or any condition or procedure that has compromised neurological control of the upper airway, are considered a contraindications for

hypoglossal nerve UAS implantation (FDA, 2014). Per Inspire Medical Systems, having a cardiac pacemaker is not a contraindication for the Inspire device.

In March 2017, the FDA approved to expand the AHI range for UAS from 20-65, to 15 to 65 events per hour (FDA, 2017). In June 2023, the FDA expanded the indications for UAS to include people with OSA who have an upper limit baseline AHI of 100 (increase from ≤65 to ≤100). The approval also increased the upper limit for recommended body mass index (BMI) to 40 (increase from ≤32 to ≤40).

The American Academy of Sleep Medicine (AASM) diagnostic criteria for OSA includes a polysomnography (PSG) showing more than 15 scorable respiratory events per hour of sleep (e.g. apnea, hypopneas, RERAs).

In June 2017, Inspire Medical Systems, Inc. announced the FDA approval for the next-generation device, Inspire 3028 implantable pulse generator, which includes magnetic resonance (MR) conditional labeling to allow patients to undergo MRI safely. The Inspire 3028 device is 40% smaller and 18% thinner than the current Inspire neurostimulator which received FDA approval in April 2014. Patients can undergo MRI on the head and extremities if certain conditions and precautions are met (Inspire Medical Systems, 2017).

Woodson et al (2018) evaluated 5-year outcomes of upper airway stimulation (UAS) from a multicenter prospective cohort study of 126 patients with OSA who were treated with UAS via a unilateral hypoglossal nerve implant. Those having continuous positive airway pressure failure with moderate to severe OSA, body mass index <32 kg/m², and no unfavorable collapse on drug-induced sleep endoscopy were enrolled in the phase 3 trial. Outcomes evaluated included apnea-hypopnea index (AHI), oxygen desaturation index, and adverse events, as well as measures of sleepiness, quality of life, and snoring. Improvement in sleepiness (Epworth Sleepiness Scale) and QOL was observed, with normalization of scores increasing from 33% to 78% and 15% to 67%, respectively. AHI response rate (AHI <20 events per hour and >50% reduction) was 75% (n = 71). "When a last observation carried forward analysis was applied, the responder rate was 63% at 5 years. Serious device-related events all related to lead/device adjustments were reported in 6% of patients". The authors concluded that improvements in sleepiness, QOL, and

respiratory outcomes were observed with 5 years of UAS. Serious adverse events were uncommon. The authors reported that "UAS is a nonanatomic surgical treatment with long-term benefit for individuals with moderate to severe OSA who have failed nasal continuous positive airway pressure".

On April 14, 2020, the FDA expanded Inspire® Upper Airway Stimulation (UAS) system indication to include adolescent patients aged 18 to 21 years.

Epiglottidectomy/Partial Epiglottidectomy

Mickelson and Rosenthal (1997) stated that OSAS is caused by narrowing of the pharyngeal airway and loss of dilator tone during sleep. In patients with severe apnea surgical correction often requires attention to both the oropharynx and hypopharynx. Tongue reduction surgery has been described for persistent apnea after failure of palatal surgery. These investigators described their experience with midline glossectomy with epiglottidectomy in 12 patients with a mean age of 48.8 +/- 14.2 years and body mass index (BMI) of 36.0 +/- 8.8 kg/m². Response to treatment was defined as a post-operative respiratory disturbance index (RDI) below 20. Three patients (25 %) responded to treatment. The mean apnea index decreased from 48.9 to 35.7, RDI decreased from 73.3 to 46.6, and lowest oxygen saturation increased from 65.9 to 77.9 %; RDI in responders decreased from 69.7 to 10. The authors concluded that midline glossectomy with epiglottidectomy has variable results, yet is effective in selected patients with hypopharyngeal narrowing related to macroglossia. This was a small study (n = 12) and only 3 patients (25 %) responded to midline glossectomy with epiglottidectomy.

Catalfumo et al (1998) OSAS is caused by obstruction or narrowing of the airway at various levels. The repair of one site only will not alleviate the syndrome if there are obstructions in other sites. Epiglottis prolapse during inspiration is an unusual cause of airway obstruction and a rare cause of OSA. These researchers presented 12 cases of OSAS due to an abnormal epiglottis. They presented their approach to the diagnosis using fiber-optic examination of the hypopharynx, and their treatment using endoscopic carbon dioxide laser partial epiglottidectomy. These investigators found in their series that in 11.5 % of patients who failed the uvulopalatopharyngoplasty procedure, the reason was a narrow airway at the hypopharyngeal

level caused by an abnormal epiglottis. They suggested that in these cases a laser partial epiglottidectomy should be performed. The authors concluded that the findings of this study showed that partial epiglottidectomy can increase the cure rate of patients with OSAS by 10 to 15 %. This was a small study (n = 12) and treatment was partial epiglottidectomy.

Golz et al (2000) noted that OSA and laryngomalacia are 2 different entities. Occasionally, they may have a common etiology: an elongated, flaccid, and lax epiglottis that is displaced posteriorly during inspiration causing airway obstruction. A total of 27 adults with a diagnosis of airway obstruction or OSA of various degrees, and 12 infants with severe stridor associated with frequent apneas due to laryngomalacia, who on fiberoptic examination were found to have a posteriorly displaced epiglottis, underwent partial epiglottidectomy with a CO₂ laser. Their post-operative recovery was uneventful. Polysomnographic studies performed after operation in the adult patients demonstrated statistically significant improvement in 85 % of the patients. In all the cases of laryngomalacia, stridor ceased permanently after surgery, together with complete cessation of the apneic episodes. The authors concluded that the findings of this study demonstrated that similar pathophysiological mechanisms may be involved in both laryngomalacia and in OSA. Effective and relatively safe treatment can be achieved by partial resection of the epiglottis with a microlaryngoscopic CO₂ laser. Again, this was a small study (n = 27) and treatment was partial epiglottidectomy.

Toh et al (2014) examined the effectiveness of combined palatal surgery and trans-oral robotic surgical (TORS) tongue base reduction with partial epiglottidectomy in the treatment of OSA in an Asian context. These investigators reported their preliminary experience with combined TORS tongue base reduction and partial epiglottidectomy with palatal surgery as a multi-level surgical treatment strategy for moderate to severe OSA in Asian patients for whom positive airway pressure treatment had failed. A retrospective study of prospectively collected data on 40 Asian patients who underwent primary TORS tongue base reduction with partial epiglottidectomy and palatal surgery for treatment of moderate to severe OSA at an academic tertiary surgical center. Twenty patients with complete pre-operative and post-operative overnight polysomnograms were evaluated for surgical success and cure, according to traditional surgical criteria, and for subjective outcome measures (snoring and satisfaction on visual analog scale [VAS] and Epworth Sleepiness Scale [ESS]) as well as complications. Traditional cure (apnea-hypopnea index [AHI]

less than 5/h) was achieved in 7 of 20 patients (35 %), traditional success (AHI less than 20 [greater than 50 % reduction in AHI]) was achieved in another 11 patients (55 %), and failure was observed in 2 patients (10 %). Subjective improvement in snoring, satisfaction, and ESS score was observed. Improvement in mean (SD) ESS score and snoring loudness on VAS were statistically significant, from 12.4 (2.87) to 6.4 (1.43) and 8.7 (0.8) to 3.5 (1.7), respectively ($p < 0.001$ for both). None of the patients needed post-operative tracheostomy. Recorded complications included tonsillar fossa bleeding, pain, temporary dysgeusia, numbness of the tongue, and temporary dysphagia. The authors concluded that trans-oral robotic surgery for tongue base reduction and partial epiglottidectomy for moderate to severe OSA in Asian patients for whom positive airway pressure treatment had failed is associated with good efficacy and low complication rates. This was a small study ($n = 40$) and combined palatal surgery and trans-oral robotic surgical tongue base reduction with partial epiglottidectomy.

Furthermore, UpToDate reviews on “Management of obstructive sleep apnea in adults” (Kryger and Mohotra, 2015) and “Overview of obstructive sleep apnea in adults” (Strohl, 2015) do not mention epiglottidectomy as a therapeutic option.

Genetic Association Studies

Varvarigou et al (2011) noted that OSA is a multi-factorial disorder with a heritable component. These researchers performed a field synopsis of genetic association studies of OSA to synthesize the available evidence. They searched multiple databases to identify studies of non-HLA genetic associations in OSA. These investigators assessed the power of the primary studies to identify odds ratios (OR) in a plausible range and performed random effects meta-analyses for genetic associations investigated by at least 3 studies. They explored the consistency of the findings between population- and family-based studies. The authors identified a total of 31 population-based case-control studies reporting allele-frequency data on 48 polymorphism-OSA associations. Sample sizes were generally small (median number of cases = 102, 25th to 75th percentile = 55 to 151; median number of controls = 79, 25th to 75th percentile = 58 to 137), and genetic effects were moderate in magnitude (median OR = 1.15, 25th to 75th percentile = 0.89 to 1.40). Studies were severely under-powered to detect ORs as high as 2; only 8 comparisons (in 6 studies) had more than 90 % power to identify a genetic effect of that magnitude at its current

sample size. Four genetic associations had been investigated in greater than or equal to 3 studies: tumor necrosis factor-alpha (TNFA)-308 A/G rs1800629, angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D), apolipoprotein E (ApoE) ε2, and APOE ε4. Only TNFA rs1800629 was significantly associated with OSA under an allele frequency model (3 studies, OR = 1.82, 95 % CI: 1.26 to 2.61). These results were robust to alternative genetic models; findings for APOE variants were consistent with those from family-based studies. The authors concluded that the developing field of OSA genetics is currently dominated by small and under-powered investigations. They stated that promising findings regarding TNFA rs1800629 need to be replicated in larger studies using more comprehensive genotyping methods.

Zhong and colleagues (2014) noted that several studies have reported that the TNF-α -308G/A polymorphism is associated with susceptibility to OSAHS. However, these results are controversial and conflicting. These researchers evaluated the association between TNF-α -308G/A and OSAHS risk by meta-analysis. Electronic databases, including PubMed, Embase, China National Knowledge Infrastructure (CNKI), Wanfang, and Weipu, were searched to identify relevant studies. Data were extracted from the included studies. A model-free approach using OR, generalized OR (ORG) and 95 % CI of the allele contrast to assess the association between the -308G/A polymorphism and OSAHS risk. Cumulative and recursive cumulative meta-analyses (CMA) were also carried out to investigate the trend and stability of effect sizes as evidence accumulated. A total of 7 studies including 1,369 OSAHS patients and 1,064 controls were identified in this meta-analysis. Significant associations were derived from the variants of the allele contrast [(OR, 1.78; 95 % CI: 1.45 to 2.18) or (ORG, 2.01; 95 % CI: 1.27 to 3.19)]. Cumulative meta-analyses showed a trend of an association. Recursive CMA indicated that more evidence is needed to conclude on the status of significance. No significant publication bias was found. The authors concluded that the findings of this meta-analysis suggested that the TNF-α -308G/A polymorphism contribute to the risk of OSAHS; further studies with larger sample should be performed to confirm these findings.

Xu and colleagues (2015) stated that ApoE gene ε2 and ε4 alleles have been reported to be associated with the risk of OSA; however, the results are controversial. Thus, these researchers performed a meta-analysis to obtain a more precise estimate of the associations by pooling sporadic, inconsistent and small-sample-size studies. Electronic databases such as PubMed and

Embase were searched to identify eligible studies focusing on the association between ApoE polymorphisms and susceptibility to OSA before April 2014. The associations were assessed by ORs with 95 % CIs. The Begg and Egger's test was used to evaluate publication bias. A total of 10 eligible studies (1,696 cases/2,216 controls for the ε2 allele and 2,449 cases/5,592 controls for the ε4 allele) were included in the meta-analysis. An association between the ApoE ε2 and ε4 alleles and OSA was not found in the overall population (OR = 0.97, 95 % CI: 0.75 to 1.25; OR = 1.09, 95 % CI: 0.86 to 0.38 for ApoE ε2 and ε4, respectively). Significant heterogeneity (ε2: I² = 36.6 %, p = 0.16; ε4: I² = 69.7 %, p = 0.001) was observed across studies, however, heterogeneity could not be explained by variations in mean age, BMI, AHI, gender, ethnic background, or the ApoE ε2 and ε4 alleles. No evidence of publication bias was found according to the Begg and Egger's test. The authors concluded that these findings showed that the ApoE ε2 and ε4 alleles have no significant associations with OSA susceptibility based on available data.

The Silent Partner OSA Appliance

The Silent Partner was designed as an alternative to CPAP therapy for the treatment of night-time snoring and/or mild-to-moderate OSA by repositioning of the mandible. It is customized for each individual patient. The SilentPartner consists of a lower tray fitted over the lower teeth, an upper tray over the upper teeth, and a mechanism to attach the lower tray to the upper tray. The device allows the practitioner to determine the advancement of the mandible and the vertical opening for desired results. This technology platform consists of a stylus, slider, and the channels into which they are placed. The device has a 10-mm long channel in the lower tray behind the anterior teeth that is perpendicular to the patient's tongue. This allows the upper component, which locks into the channel, to provide lateral excursion for the patient's comfort. Prior to final insertion, the upper and lower trays are connected together by keying the stylus into the lower channel. The device's upper component consists of a 16-mm long titanium channel into which a 9-position latched slider will let the practitioner place the stylus in the optimum position. Both the slider and the stylus are placed into the channel's frontal opening and secured into place by tension attachment.

The Silent Partner is a Class II intra-oral device cleared for marketing by the FDA through the 510(k) process; the device is substantially equivalent to the predicate devices. Moreover, there is lack of evidence that the Silent Partner is superior to standard oral appliances.

Snore Guard

Snore Guard is an oral appliance worn during sleep that resembles an athletic mouthpiece.

Suggested as a treatment for snoring, it uses normal body reflexes to maintain an open airway.

The device fits snugly on the upper teeth. When the lower jaw closes, the lower teeth close onto the lower ramp of the Snore Guard. This keeps the jaw in a normal position, rather than sagging open and back. In addition, the tongue reflexively seeks the small center orifice between the upper and lower ramp. This reflex keeps it from sagging back into the throat.

Genioplasty and Genial Tuberclle Advancement

Song and associates (2017) performed a systematic review and meta-analysis for studies evaluating genioplasty alone, genial tubercle advancement (GTA) alone, and GTA with hyoid surgery (GTA-HS) for the treatment of OSA. Three authors searched through November 15, 2015; 10 databases were used. A total of 1,207 studies were screened; 69 were down-loaded; and 13 studies met inclusion criteria. A total of 111 patients were included, with 27 standard genioplasty, 10 modified genioplasty, 24 GTA, and 50 GTA-HS patients. For standard genioplasty, the AHI reduced from a mean \pm standard deviation ($M \pm SD$) of 18.8 ± 3.8 (95 % CI: 17.6 to 20.0) to 10.8 ± 4.0 (95 % CI: 9.5 to 12.1) events/hour (relative reduction 43.8 %), $p = 0.0001$.

Genioplasty improved lowest oxygen saturation (LSAT) from 82.3 ± 7.3 % (95 % CI: 80.0, 84.7) to 86.8 ± 5.2 % (95 % CI: 85.1 to 88.5), $p = 0.0032$. For modified genioplasty AHI increased by 37.3 %. For GTA, the AHI reduced from an $M \pm SD$ of 37.6 ± 24.2 (95 % CI: 27.9 to 47.3) to 20.4 ± 15.1 (95 % CI: 14.4 to 26.4) events/hour (relative reduction 45.7 %), $p = 0.0049$. Genial tubercle advancement improved LSAT from 83.1 ± 8.3 % (95 % CI: 79.8 to 86.4) to 85.5 ± 6.8 % (95 % CI: 82.8 to 88.2), $p = 0.2789$. For GTA-HS, the AHI reduced from an $M \pm SD$ of 34.5 ± 22.1 (95 % CI: 28.4 to 40.6) to 15.3 ± 17.6 (95 % CI: 10.4 to 20.2) events/hour (relative reduction 55.7 %), $p < 0.0001$; GTA-HS improved LSAT from 80.1 ± 16.6 % (95 % CI: 75.5 to 84.7) to 88.3 ± 6.9 % (95

% CI: 86.4 to 90.2), p = 0.0017. The authors concluded that standard genioplasty, GTA and GTA-HS can improve OSA outcomes such as AHI and LSAT. Moreover, they stated that given the low number of studies, these procedures remain as an area for additional OSA research.

Furthermore, UpToDate reviews on “Management of obstructive sleep apnea in adults” (Kryger and Malhotra, 2016) and “Overview of obstructive sleep apnea in adults” (Strohl, 2016) do not mention genioplasty and genial tubercle advancement as therapeutic options.

Lateral Pharyngoplasty

Lateral pharyngoplasty is a modified form of uvulopalatoplasty where tissue from the lateral free margin of the soft palate is removed.

In a prospective, randomized study, Cahali et al (2004) compared the lateral pharyngoplasty procedure with UPPP in the treatment of OSAHS. A total of 27 adults with OSAHS originally selected for treatment with UPPP were included in this study. Patients were randomly assigned to 2 groups: (i) lateral pharyngoplasty (15 cases), and (ii) UPPP (12 cases). These researchers compared treatment outcomes through the evaluation of OSAHS-related symptoms and the analysis of polysomnographic tests and computed tomography (CT) measurements of pharyngeal airway. The lateral pharyngoplasty group achieved a statistically greater reduction in body weight, excessive daytime sleepiness (EDS), and AHI. In addition, only in this group did these investigators observe a statistically significant increase in the amount of deep sleep stages and improvement in morning headaches. Patients from the UPPP group did not present significant changes in the polysomnographic parameters. Pharyngeal airway measurement outcomes were similar in both groups and did not reflect the clinical and polysomnographic differences that were observed. The authors concluded that lateral pharyngoplasty produced better clinical and polysomnographic outcomes in the treatment of OSAHS than did UPPP, without resultant differences in the cross-sectional measurements of the pharyngeal airway between these treatments. They stated that these results may support the concept that changing the LPW (lateral pharyngeal muscular wall) properties is better than focusing on changing the pharyngeal airway size for treating patients with OSAHS.

The authors noted that there were some possible criticisms to their study -- "We do not know if our 2-dimensional CT measurements are adequately powered to identify post-operative differences in upper-airway size. The volumetric magnetic resonance imaging technique is probably more suitable for this analysis. However, the volume of tissue removed during the operation provides much more straightforward information regarding this matter than can any imaging examination. In addition, we did not monitor the inspiratory pressure during the Muller maneuver, which would have increased the value of the information on collapsibility of the upper airway but would not have altered our inclusion criteria or our analysis of the pharynx during tidal breathing. Further, controlling the patients for phase of ventilation during dynamic upper-airway imaging is important in a future study to prove that lateral pharyngoplasty effectively splints the lateral pharyngeal walls. Finally, it is always worth commenting on whether or not OSAHS is an anatomic disorder. We think that our study favors the hypothesis that OSAHS, in adults, is a pharyngeal dysfunction and not an anatomic disorder. So far, after controlling population for age and BMI, anatomy can neither differentiate healthy persons from patients with OSAHS nor assess the severity of the disease. For that purpose, we need a functional test, the polysomnography. An anatomic disorder implies an anatomic diagnosis. For instance, tonsillar hypertrophy is an anatomic disorder. To the best of our knowledge, OSAHS is not an anatomic disorder".

Caples et al (2010) noted that a substantial portion of patients with OSA seek alternatives to (PAP, the usual 1st-line treatment for the disorder. One option is upper airway surgery. As an adjunct to the American Academy of Sleep Medicine (AASM) Standards of Practice paper, these investigators conducted a systematic review and meta-analysis of literature reporting outcomes following various upper airway surgeries for the treatment of OSA in adults, including MMA, pharyngeal surgeries such as UPPP, LAUP, and RFA, as well as multi-level and multi-phased procedures. They found that the published literature comprised primarily of case series, with few controlled trials and varying approaches to pre-operative evaluation and post-operative follow-up. They included surgical morbidity and AEs where reported; but these were not systematically analyzed. Utilizing the ratio of means method, these investigators used the change in the AHI as the primary measure of effectiveness. Substantial and consistent reductions in the AHI were observed following MMA; AEs were uncommonly reported. Outcomes following pharyngeal surgeries were less consistent; AEs were reported more commonly. The authors concluded that

papers describing positive outcomes associated with newer pharyngeal techniques and multi-level procedures performed in small samples of patients appeared promising. They stated that further research is needed to better clarify patient selection, as well as safety and effectiveness of upper airway surgery in those with OSA. Furthermore, these researchers stated that the effectiveness of novel variations in pharyngeal surgery, such as extended uvulo-palatal flap (EUPF) and lateral pharyngoplasty as reported by papers from single centers are promising and warrant further investigation.

In a retrospective clinical chart review, Soares et al (2012) identified patterns of airway collapse during pre-operative drug-induced sleep endoscopy (DISE) as predictors of surgical failure following multi-level airway surgery for patients with OSAHS. Medical records of patients who underwent site-specific surgical modification of the upper airway for treatment of OSHAS were reviewed. Patients were included in this study if they had a pre-operative airway evaluation with DISE as well as pre-operative and post-operative polysomnography. Airway obstruction on DISE was described according to airway level, severity, and axis of collapse. Severe airway obstruction was defined as greater than 75 % collapse on endoscopy. Surgical success was described as a post-operative AHI of less than 20 and a greater than 50% decrease in pre-operative AHI. A total of 34 patients were included in this study. The overall surgical success rate was 56 %. Surgical success (n = 19) and surgical failure (n = 15) patients were similar with regard to age, gender, BMI, pre-operative AHI, Friedman stage, adeno-tonsillar grades, and surgical management; DISE findings in the surgical failure group demonstrated greater incidence of severe lateral oropharyngeal wall collapse (73.3 % versus 36.8 %, p = 0.037) and severe supra-glottic collapse (93.3 % versus 63.2 %, p = 0.046) as compared to the surgical success group. The authors concluded that the presence of severe lateral pharyngeal wall and/or supra-glottic collapse on pre-operative DISE was associated with OSAHS surgical failure. The identification of this failure-prone collapse pattern may be useful in pre-operative patient counseling as well as in directing an individualized and customized approach to the treatment of OSHAS. Moreover, the authors noted that "In 2003, Cahali described a lateral pharyngoplasty procedure designed to address the lateral oropharyngeal wall in patients with OSAHS. Despite the reported success compared to UPPP and few complications from this procedure, objective studies quantifying post-operative changes in lateral oropharyngeal collapse after either a UPPP or lateral pharyngoplasty are still lacking".

In a prospective study, de Paula Soares et al (2014) compared the values of 24-hour ambulatory blood pressure monitoring (ABPM) in patients with OSA, before and after lateral pharyngoplasty, and examined the influence of pre- and post-treatment polysomnographic and anthropometric variations on changes in ABPM. Arterial blood pressure with 24-hour ABPM and nocturnal polysomnography were measured before and 6 months after surgery in 18 consecutively evaluated adults with OSA at a tertiary center. A total of 83.3 % were normotensive patients.

Nocturnal measurements showed a decrease of 5.3 mmHg in mean arterial pressure (MAP; p = 0.01), 7.4 mmHg in mean arterial systolic pressure (SP; p = 0.006), and 4.2 mmHg in mean arterial diastolic pressure (DP; p = 0.03), leading to significant reductions in all 24-hour measurements: 3.6 mmHg in MAP, 4.8 mmHg in SP, and 2.9 mmHg in DP. There were also significant mean reductions in the AHI, from 33.5 to 20.9 (p = 0.02), arousal index, from 31.6 to 16.7 (p = 0.005), and percentage of total sleep time with oxyhemoglobin saturation less than 90 %, from 10.6 % to 0.9 % (p = 0.008). No correlations were noted between the measurements of arterial blood pressure and polysomnographic or anthropometric variations. The authors concluded that in this small case series, lateral pharyngoplasty reduced the values obtained in the 24-hour ABPM due to a significant reduction of blood pressures during sleep in patients with OSA 6 months after surgery. Moreover, they noted that although the patients presented with reductions in AHI, arousals, and desaturation time, this was not correlated with the improvement in arterial blood pressure.

This study had several drawbacks: (i) small sample size (n = 18) and the lack of a control group precluded generalizations about the impact of lateral pharyngoplasty on systemic arterial hypertension, (ii) the selection bias of surgical cases made comparisons with other studies difficult, as these researchers excluded cases of morbid obesity or with more pronounced cardiovascular co-morbidities, which represent populations typically assessed by other studies with CPAP, and (iii) ABPM and the polysomnography were done on different nights, which can be seen as a weakness of the study because the sleep periods were not objectively measured; but only reported by the patients during ABPM. The literature already showed that monitoring blood pressure during sleep can interfere with the sleep test by increasing the arousals, which is not desirable. These investigators could verify that there was little or no difference in the subjects' weight between those examinations, either before or after the surgeries, but they could not be sure that the OSA has not worsened between the pre-operative sleep

studies and the surgeries. The proximity of pre-operative ABPM to the day of the surgery, which is a stressful time for the patient, could have increased that blood pressure measurement, falsely improving the results of post-operative ABPM. However, given the significant reduction in blood pressure observed during sleep but not during wakefulness, the authors believed that this factor had little interference with their results.

Chi et al (2015) examined factors contributing to OSAS and identified the different severity categories of OSA that could benefit from lateral pharyngoplasty. These researchers included 60 patients undergoing UPPP with or without lateral pharyngoplasty from December 1, 2008 to May 31, 2012; 6 who did not complete the post-operative survey were excluded. A total of 54 subjects were assigned alternatively to either UPPP alone (control group, n = 29) or to UPPP with lateral pharyngoplasty (intervention group, n = 25). The reduction of AHI in the intervention group (49.3 %) was higher than it was in the control group (30.4 %), but the average value was not statistically significant ($p = 0.088$). Only patients with moderate OSA in the intervention group achieved a significant reduction of AHI (30.7 versus 10.8 %; $p = 0.020$). Factors such as BMI, nadir/mean SpO₂, snoring index, ESS and periodic limb movement index did not change significantly following lateral pharyngoplasty. These investigators employed cephalometry to evaluate patients' upper airway anatomy, and found that the retroglossal space played a critical role in severe OSA. The authors concluded that the findings of this study showed that only patients in the moderate category could benefit from adding lateral pharyngoplasty to UPPP; however, patients in the mild or severe category did not benefit from adding this procedure. This was a small ($n = 25$) study; and only some of the subjects (those with moderate category) in the intervention group benefited from the addition of lateral pharyngoplasty. These preliminary findings need to be validated by well-designed studies.

Dizdar et al (2015) noted that snoring is caused by the vibration of structures of the oral cavity, such as the soft palate, uvula, tonsils, base of the tongue, epiglottis, and lateral pharyngeal walls. When these structures collapse and obstruct the airway, apnea occurs; OSAS is characterized by repeated periods of upper airway obstruction, a decrease in arterial oxygen saturation, and interrupted sleep. The prevalence of OSAS is 1 % to 5 % in men and 1.2 % to 2.5 % in women. Crucial factors in deciding the surgical approach include a detailed ear-nose-throat examination, Muller maneuver, sleep endoscopy, and AHI scores. Accepted treatments include CPAP,

surgeries of the base of the tongue and/or palate, and multi-level surgeries. However, it is important to evaluate the effectiveness of these procedures. The authors evaluated the outcomes of 23 patients who underwent surgery for OSAS, using pre-operative and post-operative PSG and the ESS. The results were compared before and after surgery. In all, 14 patients had lateral pharyngoplasty and 9 had UPPP. The PSG and ESS values were significantly lower in both groups, post-operatively. Patients indicated that their quality of life had improved. The authors concluded that the surgeries were successful. They stated that these findings indicated that lateral pharyngoplasty and UPPP can be used in appropriate patients; and longer-term studies on more patients will provide more detailed information in the future.

Karakoc et al (2015) evaluated the effect of different types of such surgical procedures including expansion sphincter pharyngoplasty (ESP), lateral pharyngoplasty (LP), and anterior palatoplasty (AP) on nasalance scores. A total of 49 consecutive patients with primary snoring or OSA who underwent AP, LP, and ESP procedures were included in this study. All patients underwent a fully attended overnight PSG and detailed otolaryngologic examination. Nasalance studies were performed with Nasometer II instrument by reading 3 passages that were categorized according to the amount of nasal consonants (oral, oro-nasal, and nasal passages), pre-operatively, and 3 months after surgery. There was no statistically significant difference in either group between pre-operative and post-operative assessments of nasalance scores for all 3 passages; 7 patients experienced nasal regurgitation symptoms for fluids for a short time after LP, 2 patients after AP, and 7 patients after ESP. None of these symptoms showed persistence and diminished approximately at 1-month follow-up. The authors concluded that AP, LP, and ESP did not appear to have any impact on nasalance scores of males.

Mandibular Distraction Osteogenesis

Tsui and colleagues (2016) performed a systematic review to answer the clinical question "What are the effectiveness of mandibular distraction osteogenesis (MDO) and its complications to treat patients with OSAS?". Relevant articles on MDO were assessed and selected in 3 rounds for final review based on 5 pre-defined inclusion criteria and followed by a round of critical appraisal. Different types of distraction and their treatment outcomes of OSAS were recorded with standardized form and analyzed. A total of 12 articles were included in the final review. A total of

256 patients aged 7 days to 60 years were treated with either external or internal MDO, with a mean follow-up period of 6 to 37 months. The average distraction distance of 12 to 29mm was achieved with various distraction protocols. The success rate for adult patients was 100 %, and cure rates were ranged from 82 % to 100 %. The definition of success or cure for OSAS in children or infants was not defined. Therefore, there were no clearly reported success or cure rates for children/infants in the included studies. However, all studies reported that these patients showed significant improvement in OSAS, with many of them who avoided tracheostomy or had the tracheostomy decannulated. The complication rates were ranged from 0 % to 21.4 %, with most being from local wound infections or neurosensory disturbances. The authors concluded that this systematic review showed that MDO was effective in resolving OSAS in adults with retrognathic mandible; and MDO also showed promising results in infants or children with OSAS. From the results of this systematic review, these investigators recommended to define the criteria of success or cure for OSAS surgery in children and infants. They also recommended setting up randomized controlled trials (RCTs) to compare MDO with traditional maxilla-mandibular advancement surgery for OSAS patients and to provide a better evidence on the success and complication rates of the techniques.

Furthermore, UpToDate reviews on “Management of obstructive sleep apnea in adults” (Kryger and Malhotra, 2016) and “Overview of obstructive sleep apnea in adults” (Strohl, 2016) do not mention distraction osteogenesis as a management tool.

Remotely Controlled Mandibular Positioner

Kastner and associates (2016) performed a review of the current evidence regarding the use of a remotely controlled mandibular positioner (RCMP) and analyzed the effectiveness of RCMP as a predictive selection tool in the treatment of OSA with oral appliances that protrude the mandible (OAm), exclusively relying on single-night RCMP titration. An extensive literature search is performed through PubMed.com, Thecochanelibrary.com (CENTRAL only), Embase.com, and recent conference meeting abstracts in the field. A total of 254 OSA patients from 4 full-text articles and 5 conference meeting abstracts contributed data to the review. Criteria for successful RCMP test and success with OAm differed between studies. Study populations were not fully comparable due to range-difference in baseline AHI. However, in all studies elimination of airway

obstruction events during sleep by RCMP titration predicted OAm therapy success by the determination of the most effective target protrusive position (ETPP). A statistically significant association is found between mean AHI predicted outcome with RCMP and treatment outcome with OAm on polysomnographic or portable sleep monitoring evaluation ($p < 0.05$). The authors concluded that existing evidence regarding the use of RCMP in patients with OSA indicated that it might be possible to protrude the mandible progressively during sleep under polysomnographic observation by RCMP until respiratory events are eliminated without disturbing sleep or arousing the patient. They noted that ETPP as measured by the use of RCMP was significantly associated with success of OAm therapy in the reported studies. They stated that RCMP might be a promising instrument for predicting OAm treatment outcome and targeting the degree of mandibular advancement needed.

Compliance Monitor for Oral Appliances

The American Academy of Sleep Medicine (AASM) and the AADSM's clinical practice guideline on "The treatment of obstructive sleep apnea and snoring with oral appliance therapy" (Ramar et al, 2015) stated that "There are several recent non-RCTs published that report on the use of objective adherence monitors in OAs. Further RCTs are needed to evaluate the efficacy of these monitors and also to compare it with the CPAP objective adherence rate".

Furthermore,, an UpToDate reviews on "Oral appliances in the treatment of obstructive sleep apnea in adults" (Cistulli, 2017) does not mention the use of compliance monitors.

Rapid Maxillary Expansion

Machado-Junior and colleagues (2016) conducted a meta-analysis on the use of rapid maxillary expansion (RME) to treat OSAS in children. These investigators performed a literature survey using PubMed and Medline for English articles published up to December 2014 with the following descriptors: Sleep apnea, obstructive, children, treatment, orthodontic, othopaedic, maxillary expansion. Studies were included in the meta-analysis if they were case-controlled studies, randomized, and involved non-syndromic children aged 0 to 12 years old diagnosed with OSA by the polysomnography AHI before and after the intervention, submitted RME only. In all, 10 articles conformed to the inclusion criteria and were included in this meta-analysis. The total

sample size across all these articles was 215 children, having a mean age of 6.7 years, of whom 58.6 % were male. The mean AHI during the follow-up was -6.86 ($p < 0.0001$). The authors concluded that RME in children with OSAS appeared to be an effective treatment for this syndrome. Moreover, they stated that further randomized clinical studies are needed to determine the effectiveness of RME in adults.

Camacho and associates (2017) performed a systematic review with meta-analysis for sleep study outcomes in children who have undergone RME as treatment for OSA. Three authors independently reviewed the international literature through February 21, 2016. A total of 17 studies reported outcomes for 314 children (7.6 ± 2.0 years old) with high-arched and/or narrow hard palates (transverse maxillary deficiency) and OSA. Data were analyzed based on follow-up duration: less than or equal to 3 years (314 patients) and greater than 3 years (52 patients). For less than or equal to 3-year follow-up, the pre- and post-RME AHI decreased from a mean \pm standard deviation ($M \pm SD$) of $8.9 \pm 7.0/\text{hr}$ to $2.7 \pm 3.3/\text{hr}$ (70 % reduction). The cure rate (AHI less than 1/hr) for 90 patients for whom it could be calculated was 25.6 %. Random effects modeling for AHI standardized mean difference (SMD) is -1.54 (large effect). Lowest oxygen saturation (LSAT) improved from $87.0 \pm 9.1\%$ to $96.0 \pm 2.7\%$. Random effects modeling for LSAT SMD is 1.74 (large effect). AHI improved more in children with previous adenotonsillectomy or small tonsils (73 to 95 % reduction) than in children with large tonsils (61 % reduction). For greater than 3-year follow-up (range of 6.5 to 12 years), the AHI was reduced from an $M \pm SD$ of $7.1 \pm 5.7/\text{hr}$ to $1.5 \pm 1.8/\text{hr}$ (79 % reduction). The authors concluded that improvement in AHI and lowest oxygen saturation had consistently been seen in children undergoing RME, especially in the short term (less than 3-year follow-up). Moreover, they stated that randomized trials and more studies reporting long-term data (greater than or equal to 3-year follow-up) would help determine the effect of growth and spontaneous resolution of OSA.

Chang and colleagues (2020) stated that further studies of maxillary skeletal expander (MSE) are needed to confirm the effectiveness of this therapeutic approach across a larger number of adult patients. Because of its reduced costs and far fewer risks compared to alternative therapeutic options, this novel mini-implant assisted rapid maxillary expansion (MARME) design and protocol offer great promise for the future of non-surgical maxillary orthopedic expansion and minimally invasive treatment for OSA in adult patients.

Voxel-Based Brain Morphometry Studies

Shi and co-workers (2017) noted that gray matter (GM) anomalies may represent a critical pathology underlying OSA. However, the evidence regarding their clinical relevance is inconsistent. These researchers conducted a meta-analysis of voxel-based morphometry (VBM) studies of patients with OSA to identify their brain abnormalities. A systematic search was conducted based on PRISMA guidelines, and a meta-analysis was performed using the anisotropic effect-size-based algorithms (ASE-SDM) to quantitatively estimate regional GM changes in patients with OSA. A total of 15 studies with 16 datasets comprising 353 untreated patients with OSA and 444 healthy controls were included. The results revealed GM reductions in the bilateral anterior cingulate/para-cingulate gyri (ACG/ApCG), left cerebellum (lobules IV/V and VIII), bilateral superior frontal gyrus (SFG, medial rostral part), right middle temporal gyrus (MTG), and right premotor cortex. Moreover, GM reductions in the bilateral ACG/ApCG were positively associated with BMI and age among patients with OSA, and GM reductions in the SFG (medial rostral part) were negatively associated with ESS scores and sex (male). These abnormalities may represent structural brain underpinnings of neurocognitive abnormalities and respiratory-related abnormalities in OSA. The authors concluded that the findings of this study added to psycho-radiology, which is a promising subspecialty of clinical radiology mainly for psychiatric disorders. Moreover, they stated that further exploration is needed to verify the conclusions through multi-modality neuroimaging studies and longitudinal studies and to determine their clinical relevance for clinical practice in the diagnosis and management of patients with OSA.

The authors stated that this study had several drawbacks: (i) this meta-analysis was coordinate-based, and this approach has some inherent inaccuracies compared with image-based meta-analyses, (ii) the results may be biased because different studies used different statistical thresholds and different criteria for OSA diagnoses, (iii) the jack-knife sensitivity analysis revealed that the findings of GM reductions in the right premotor cortex, left cerebellar lobules and right MTG were less robust than alterations in other brain regions; thus, these findings should be interpreted with caution, (iv) although most researchers carefully excluded co-morbid diseases or sleep disorders and treatment history, participant heterogeneity remained that may have biased the results, such as those regarding the severity, duration and cause of OSA; the degree of nocturnal desaturation; the presence of

predominant apneas or hypopneas; and sleep quality, and (v) the small cohorts of some of the included studies might have biased the results.

Screening for Asymptomatic Obstructive Sleep Apnea

Based on data from the 1990s, estimated prevalence of OSA in the United States is 10 % for mild OSA and 3.8 % to 6.5 % for moderate-to-severe OSA; current prevalence may be higher, given the increasing prevalence of obesity. Severe OSA is associated with increased all-cause mortality, cardiovascular disease and cerebrovascular events, diabetes, cognitive impairment, decreased quality of life, and motor vehicle crashes. The US Preventive Services Task Force reviewed the evidence on the accuracy, benefits, and potential harms of screening for OSA in asymptomatic adults seen in primary care, including those with unrecognized symptoms. The USPSTF also evaluated the evidence on the benefits and harms of treatment of OSA on intermediate and final health outcomes. The USPSTF found insufficient evidence on screening for or treatment of OSA in asymptomatic adults or adults with unrecognized symptoms. Thus, the USPSTF was unable to determine the magnitude of the benefits or harms of screening for OSA or whether there is a net benefit or harm to screening. The USPSTF concluded that the current evidence is insufficient to evaluate the balance of benefits and harms of screening for OSA in asymptomatic adults.

Drug-Induced Sleep Endoscopy (DISE)

Drug-induced sleep endoscopy (DISE), also known as sleep nasoendoscopy or nasopharyngoscopy, is an upper airway evaluation technique which uses a flexible fiberoptic endoscope to examine the site of airway obstruction while individuals are in a sedative-induced sleep designed to mimic the natural sleep state. The purpose of DISE is to determine what causes site of airway obstruction during sleep and help surgeons determine and plan appropriate surgical procedures for their patients with OSA who have failed, or were unable to tolerate, positive airway pressure (e.g., CPAP or BIPAP) (Schwab, 2016; Zapanta, 2018). DISE is usually performed in the operating room which makes it difficult to use as an imaging modality in large clinical studies (Schwab, 2016).

In a retrospective chart review, Lan and colleagues (2015) reviewed DISE findings and correlated the patterns of airway collapse with BMI and objective sleep study respiratory variables, with particular emphasis on oxygen desaturation variables. From January 2010 to March 2014, a total of 64 patients underwent DISE, and its findings were registered using the VOTE (velum, oropharynx, tongue base, epiglottis) classification system. Associations were analyzed between DISE, BMI, and polysomnographic parameters. Complete lateral oropharyngeal collapse was significantly associated with increased severity of OSA, reflected by a higher oxygen desaturation index, AHI, apnea index, the percent of the total time with oxygen saturation level lower than 90 %, and minimal oxygen saturation. Complete concentric collapse of the velum and complete lateral oropharyngeal collapse were associated with higher BMI values. The authors concluded that the findings of this study demonstrated a strong association between complete lateral oropharyngeal wall collapse and increased OSA severity, particularly with objective oximetry measures. Patients with a complete lateral oropharyngeal wall collapse may need aggressive treatment strategies because of the high probability of subsequent cardiovascular complications (Level of Evidence = IV).

The authors stated that this study had several drawbacks – “Among 64 patients, 2 received home sleep tests; however, in both, all variables involved were reported. Previous studies suggested that there is good agreement between respiratory variables on home sleep tests and standard PSG. Due to the subjective nature of DISE, it may be inherently prone to inconsistencies; however, previous studies have reported acceptable consistency for DISE. Kezirian et al found that the inter-rater reliability of DISE is moderate to substantial. Another study by Rodriguez-Bruno et al reported that test-retest reliability of DISE appears to be good. A number of factors (e.g., experience of the performing surgeon, depth of sedation, or the drug used for sedation) may influence the findings seen on DISE. In our study, we tried to limit the impact of these factors by using the same drug for all of our patients, and all DISEs were evaluated only by an experienced surgeon. Also, because only patients who were not CPAP compliant and who were evaluated for further surgery or oral appliances underwent DISE, these findings may not be generalized to all patients with OSA. Furthermore, another limitation of the study was the lack of blinding. The author rating the videos was not blinded to the sleep study variables, and because DISE is a partially subjective assessment, the results could be biased”.

Ong et al. (2017) conducted a single-blind cross-sectional study to evaluate the application of DISE in patients treated with UAS therapy. The authors' aim was to determine the level of agreement among experienced operators of candidacy for UAS based on evaluation from the DISE procedure. Four otolaryngologists with extensive DISE experience were given 63 video clips from the STAR trial video library. These videos were graded using the VOTE classification. Percentage agreement and Cohen's κ (for inter-rater reliability) were calculated between pairs of reviewers, assessing palatal complete concentric collapse (CCC) and determining UAS eligibility. Subjects were also grouped based on collapse severity for each reviewer. The reviewers were approximately 90 percent in agreement on findings at the level of the soft palate and tongue base. The inter-rater reliability for palatal CCC ranged from moderate to substantial. The agreement on determining the criteria for UAS implantation ranged from poor to moderate. All 4 upper airway structures as classified by the criteria of the VOTE were graded by all the reviewers as contributing to obstruction in a majority of subjects who were performed via application of DISE. The authors concluded that "application of DISE remains a subjective examination, even among those experienced operators, therefore more studies need to be performed for evaluation of improvement in inter-rater reliability after implantation of training videos".

Atkins and Mandel (2018) reviewed the role of DISE to assist those preparing to establish a DISE program. The authors note that new developments in surgical approaches to OSA have stimulated increased interest and demand for drug-induced sleep endoscopy. New techniques include transoral robotic surgery and hypoglossal nerve stimulation. Recent DISE literature has sought to address numerous debates including relevance of DISE findings to those during physiologic sleep and the most appropriate depth and type of sedation for DISE. The authors state that the role of DISE in surgical evaluation and planning for treatment of OSA continues to develop. Numerous questions as to the optimal anesthetic approach remain unanswered.

Multicenter studies that employ a standardized approach using EEG assessment, pharmacokinetic-pharmacodynamic modelling, and objectively defined clinical endpoints will be helpful.

The DISE procedure is currently listed as one of the criteria for evaluation of medical necessity for the FDA-approved hypoglossal nerve neurostimulation (e.g., Inspire II System, Inspire 3028 system for Upper Airway Stimulation (UAS) Therapy). See "Hypoglossal Nerve Stimulation".

Glossectomy for Obstructive Sleep Apnea (OSA)

Vicini et al (2017) reviewed TORS for the treatment of OSA-hypopnea syndrome (OSAHS). The review presented the experience of the robotic center that developed the technique with regards to patient selection, surgical method, and post-operative care. In addition, the review provided results of a systematic review and meta-analysis of the complications and clinical outcomes of TORS when applied in the management of OSAHS. The rate of success, defined as 50 % reduction of pre-operative AHI and an overall AHI less than 20 events/hour, was achieved in up to 76.6 % of patients with a range between 53.8 % and 83.3 %. The safety of this approach was reasonable as the main complication (bleeding) affected 4.2 % of patients (range of 4.2 % to 5.3 %). However, transient dysphagia (7.2 %; range of 5 % to 14 %) did compromise the quality of life (QOL) and must be discussed with patients pre-operatively. The authors concluded that TORS for the treatment of OSAHS appeared to be a promising and safe procedure for patients seeking an alternative to traditional therapy. They stated that appropriate patient selection remains an important consideration for successful implementation of this novel surgical approach requiring further research. The keywords of this study included midline glossectomy, obstructive sleep apnea, partial glossectomy, posterior glossectomy, sleep surgery, TORS, and transoral robotic surgery.

In a retrospective study, Folk and D'Agostino (2017) compared sleep-related outcomes in OSAHS patients following base of tongue resection via robotic surgery and endoscopic midline glossectomy. A total of 114 robotic and 37 endoscopic midline glossectomy surgeries were performed between July 2010 and April 2015 as part of single or multi-level surgery. Patients were excluded for indications other than sleep apnea or if complete sleep studies were not obtained. Thus, 45 robotic and 16 endoscopic surgeries were included in the analysis. In the robotic surgery group there were statistically significant improvements in AHI [(44.4 ± 22.6) events/hour - (14.0 ± 3.0) events/hour, $p < 0.001$], Epworth Sleepiness Scale (12.3 ± 4.6 to 4.5 ± 2.9, $p < 0.001$), and O₂ nadir (82.0 % ± 6.1 % to 85.0 % ± 5.4 %, $p < 0.001$). In the endoscopic group there were also improvements in AHI (48.7 ± 30.2 to 27.4 ± 31.9, $p = 0.06$), Epworth Sleepiness Scale (12.6 ± 5.5 to 8.3 ± 4.5, $p = 0.08$), and O₂ nadir (80.2 % ± 8.6 % to 82.7 % ± 6.5 %, $p = 0.4$). Surgical success rate was 75.6 % and 56.3 % in the robotic and endoscopic groups, respectively. Greater volume of tissue removed was predictive of surgical success in the robotic

cases (10.3 versus 8.6 ml, p = 0.02). The authors concluded that both robotic surgery and endoscopic techniques for tongue base reduction improved objective measures of sleep apnea; greater success rates may be achieved with robotic surgery compared to traditional methods. Moreover, they stated that these findings were limited by the retrospective nature of this study, and further clinical studies are needed despite these encouraging results.

Measurements of Central Corneal Thickness, Intra-Ocular Pressure, and Retinal Nerve Fiber Layer Thickness for Grading Severities of Obstructive Sleep Apnea Syndrome (OSAS)

Wang and colleagues (2017) noted that many studies have assessed the changes of retinal nerve fiber layer (RNFL) thickness in patients with OSAS, but the results were inconsistent. These researchers performed a meta-analysis to evaluate the RNFL changes in OSAS measured *in-vivo*. Pertinent studies were identified by a comprehensive search of PubMed, Embase, Web of science, Cochrane library, Scopus, and Chinese biomedical disc databases from inception to August 2016. A fixed effects model was used to pool the weighted mean difference (WMD) and 95 % CI between OSAS group and control group. A total of 17 studies were included in the final analysis, with 12 for descriptive analysis and 5 for meta-analysis, involving a total of 1,757 eyes (1,106 in the OSAS group and 651 in the control group). The RNFL in OSAS was significantly lower than control group, with pooled WMD -3.53 (95 % CI: -4.80 to -2.26, p < 0.001) for average RNFL, -3.69 (95 % CI:-5.49 to -1.89, p < 0.001) for superior RNFL, -4.66 (95 % CI: -6.92 to -2.39, p < 0.001) for inferior RNFL, -3.15 (95 % CI:-5.19 to -1.10, p = 0.003) for nasal RNFL, and -2.45 (95 % CI: -4.59 to -0.31, p = 0.025) for temporal RNFL. Along with severities of OSAS, a trend of more profound reduction of average RNFL was observed in advanced OSAS, with WMD of average RNFL thickness -1.75 (95 % CI:-4.47 to -0.98, p = 0.209) for mild OSAS, -3.54 (95 % CI:-6.33 to -0.73, p = 0.013) for moderate OSAS, and -7.17 (95 % CI:-10.00 to -4.34, p < 0.001) for severe OSAS. The majority of studies in the descriptive review demonstrated similar findings. The authors concluded that OSAS was associated with a reduced RNFL in all quadrants compared to controls. They stated that evaluation of RNFL may serve as a tool for grading severities of OSAS. However, considering the limited evidence, the conclusions should be interpreted cautiously.

In a prospective study, Teberik and associates (2018) evaluated the intra-ocular pressure (IOP), central corneal thickness (CCT), and peri-papillary RNFL thickness in patients with OSAS. A total of 103 patients with OSAS (study group) and 37 healthy subjects were enrolled. All participants underwent comprehensive ophthalmic examinations. Main outcome measures were IOP by Goldmann applanation tonometry, CCT measurement using ultrasound (US) pachymetry and peri-papillary RNFL thickness measured by spectral-domain optical coherence tomography (SD-OCT). The differences between the mean values of RNFL thickness in all quadrants were similar in both groups and were not statistically significant ($p = 0.274$). The IOP and CCT measurement averages of all patients with OSAS were lower than the control group. However, these differences were not statistically significant. There was no correlation between the AHI, lowest oxygen saturation (LAST) or BMI and the peri-papillary RNFL thickness, IOP or CCT when OSAS group was divided by severity. The authors concluded that the findings of this study suggested that peri-papillary RNFL thickness, IOP or CCT did not differ significantly between OSAS and control groups. These researchers also found no correlation between AHI, LAST and BMI and RNFL, CCT and IOP.

Measurements of Fas-Positive Lymphocytes for Evaluation of Systemic Inflammation in OSAS

Domagala-Kulawik and colleagues (2019) noted that OSAS is associated with alterations in immune system that may lead to serious complications. These researchers examined lymphocyte populations in OSAS with special attention to the Fas-positive cells. A total of 51 patients with confirmed OSA and 20 healthy subjects were investigated. The OSA severity indices, data concerning co-morbidities, and markers of inflammation and metabolic disorders were collected. Flow cytometry was used to analyze the lymphocyte profile and expression of Fas receptors (CD95). Concentration of adiponectin, IL-1 β , TNF- α , and soluble form of Fas (sFas) were measured. Proportions of Fas-positive cells in the pool of CD4+ and Fas-positive in the pool of CD8+ cells in the blood of patients were significantly increased when compared with healthy subjects (74.5 % versus 65.6 % and 78.8 % versus 70.9 %, respectively, $p < 0.05$). No correlation with OSA severity was found. However, the proportion and number of Fas+ cells were elevated in obese patients, in non-smokers, and in patients suffering from COPD and hypertension. There were several significant relations of Fas+ cells with inflammatory markers of

systemic inflammation. The authors concluded that lymphocytes with the expression of Fas receptor were associated with systemic inflammation in OSAS. These investigators stated that the major weakness of this study was that they did not perform functional analysis of Fas-positive lymphocytes. These researchers presented for the first time the association of Fas-positive lymphocytes with the systemic inflammation of OSAS.

Upper Gastro-Intestinal Endoscopy for Diagnosing Obstructive Sleep Apnea Syndrome

Ohata and colleagues (2019) stated that despite the high prevalence of OSAS, most individuals are unaware of its diagnosis. These researchers examined if an upper gastro-intestinal (GI) endoscopy can accurately predict the incidence of OSAS. After endoscopic evaluation of laryngo-pharyngeal collapse, a total of 154 subjects with laryngo-pharyngeal collapse and 52 control subjects underwent PSG. Based on the modified Fujita Classification, upper airway obstruction was classified into 3 different types: oropharyngeal, supra-glottic, and combined type, and associations between upper airway obstruction and OSAS were evaluated. Of 154 subjects with laryngo-pharyngeal collapse, 108 (70.1 %) were diagnosed as OSAS, while only 4 (7.7 %) control subjects were diagnosed as OSAS ($p < 0.001$). The sensitivity and specificity of endoscopic diagnosis were 96.4 and 51.1 %, respectively. Oropharyngeal involvement was frequently found in 90.2 % of the subjects (139/154). The severity of upper airway obstruction was significantly correlated with the AHI score ($r = 0.55$, $p < 0.001$). A multi-variate logistic regression analysis revealed that a male sex (OR 5.20; 95 % CI: 2.65 to 10.2, $p < 0.001$), BMI of greater than or equal to 25 kg/m² (OR 4.98; 95 % CI: 2.23 to 11.2, $p = 0.02$) and severe obstruction (OR 7.79; 95 % CI: 3.34 to 18.2, $p < 0.001$) were significant independent predictors of severe OSAS. The authors concluded that a conventional upper GI endoscopy might be useful as a diagnostic modality for OSAS. These preliminary findings need to be validated by well-designed studies.

Use of Serum Level of Advanced Glycation End Products and Obstructive Sleep Apnea-Hypopnea Syndrome

In a meta-analysis, Wu and co-workers (2018) examined the difference in the serum level of advanced glycation end-products (AGEs) between patients with OSAHS and controls. These investigators carried out a systematic literature search using PubMed, Elsevier, SCI, Wanfang, Weipu, and China National Knowledge Internet. Eligible studies that reported the serum AGE

level in patients with OSAHS were identified by 2 reviewers. Review Manager version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and R version 3.10 (www.r-project.org) were employed for data synthesis. A total of 5 studies involving 670 subjects were identified. The meta-analysis showed that the mean serum AGE level in the OSAHS group was 0.98 mmol/L higher than those in the control group (95 % CI: 0.69 to 1.27). The authors concluded that the findings of this meta-analysis showed that the serum AGE level was elevated in patients with OSAHS; suggesting that AGEs may play an important role in insulin resistance in OSAHS and serve as a biomarker for patients with OSAHS with a high risk of type 2 diabetes mellitus.

The authors stated that this study had several drawbacks. First, the meta-analysis included 5 case-control trials, each of which might have had a degree of experimental bias. Second, the sample size was relatively low, which may have affected the accuracy of these findings. Larger studies would allow for more accurate effect size estimation and sophisticated moderator analysis. Third, although moderate heterogeneity was present among the individual studies, the exact source of the heterogeneity could not be identified from the limited number of studies.

Devices for Positional Therapy (e.g., the Lunoa System) for the Treatment of Positional OSA

In a prospective, multi-center cohort study, van Maamen and de Vries (2014) examined the effectiveness, long-term compliance, and effects on subjective sleep of the Sleep Position Trainer (SPT) in patients with mild-to-moderate position-dependent OSAS (POSAS). Patients were asked to use the SPT for 6 months. At baseline and after 1, 3, and 6 months, questionnaires would be completed: ESS, FOSQ, Pittsburgh Sleep Quality Index (PSQI), and questions related to SPT use. A total of 145 patients were included; SPT use and SPT data could not be retrieved in 39 patients. In the remaining 106 patients, median percentage of supine sleep decreased rapidly during SPT's training phase (day 3 to 9) to near-total avoidance of supine sleep. This decrease was maintained during the following months of treatment (21 % at baseline versus 3 % at 6 months); SPT compliance, defined as more than 4 hours of nightly use, was 64.4 %. Regular use, defined as more than 4 hours of usage over 5 nights/week, was 71.2 %. Subjective compliance and regular use were 59.8 % and 74.4 %, respectively. Median ESS (11 to 8), FOSQ

(87 to 103) and PSQI (8 to 6) values significantly improved compared with baseline. The authors concluded that PT using the SPT effectively diminished the percentage of supine sleep and subjective sleepiness and improved sleep related QOL in patients with mild-to-moderate POSAS.

SPT treatment appeared to have sustained effects over 6 months, and SPT compliance and regular use rate were relatively good. Subjective and objective compliance data corresponded well. However, these researchers stated that the lack of a placebo-controlled group limited the efficacy of conclusions. They stated that future research needs to focus on objective long-term treatment effects, especially in relation to other already generally accepted POSAS treatment modalities.

The authors stated that this study had several drawbacks. A total of 145 patients were included in our study; 39 did not register their SPT in the online database. No SPT use or SPT data could be retrieved in these patients, despite implementation of protocolled safety nets; registered patients would receive an email reminding them to fill out the questionnaires in case they had not done so in time. When designing this trial, the possibility of patients not registering online was not fully taken into account. SPT instructions and delivery were taken care of by a Dutch medical device distributor company. The process of registering online was left to the patient, which was not ideal from a research perspective in hindsight. However, the results of this study, in terms of follow-up potential, were likely a good reflection of clinical reality. Of these 106 patients, only 53 patients uploaded their SPT data for the full study period and filled in the questionnaires at 2 or more time-points. Patients did not receive any other incentives to fill out the questionnaires or upload their data. The data retrieved over the full 6 months might therefore have resulted in a positive selection bias, showing merely the best SPT users. However, some patients reportedly stopped using the SPT because they felt better, no longer had any subjective complaints, and learned to avoid sleeping in the supine position. These investigators were unable to collect their experiences in the questionnaires because most of these patients had already stopped using the SPT in the first weeks of use and were therefore lost to follow-up. Any potential learning effect of PT in general or in sleeping with the SPT remains to be investigated. Also, this study lacked objective measures on treatment efficacy by means of a repeat PSG in all patients to evaluate effects on AHI and snoring. Although effects of SPT use on AHI have been reported before, effects of the SPT on snoring remain to be investigated. Another drawback of this study was the lack of a control group; these findings and conclusions could have been stronger and more

valuable had the authors compared the SPT users to a group of patients with POSAS with another treatment regimen. Furthermore, this study lacked an educational program or positive reinforcement program for the patients. Loss to follow-up would probably have been less and compliance would probably have been higher given the positive results in trials with CPAP users.

In a systematic review and meta-analysis, Barnes and colleagues (2017) examined the effectiveness of positional modification techniques in preventing supine sleep, sleep-disordered breathing and other clinically important outcomes in patients with supine OSA; RCTs comparing positional modification techniques (means to keep people sleeping on their side) with any other therapy or placebo were included. These researchers carried out electronic searches of databases including CENTRAL, Medline, CINAHL, Embase, and Web of Science up to April 2016.

Meta-analysis was undertaken where possible. This comprehensive meta-analysis found benefit for positional modification techniques in those with supine OSA in terms of reduction in AHI and time spent supine. While positional modification techniques were effective in terms of a reduction in AHI, CPAP was more effective than these techniques. The authors concluded that a reliable diagnosis of supine OSA should be considered, and further research is needed on patient-centered outcomes including comfort, barriers to adherence, cost-analysis, and long-term outcomes including the effect on cardiovascular disease, the metabolic syndrome, and insulin resistance.

Ravesloot and associates (2017) stated that in about 56 % to 75 % of patients with OSA, the frequency and duration of apneas are influenced by body position. This is referred to as position-dependent OSA or POSA. Patients with POSA can be treated with a small device attached to either the neck or chest. These devices -- a new generation of devices for PT -- provide a subtle vibrating stimulus that prevents patients adopting the supine position. In a systematic review and meta-analysis, these investigators examined if PT is effective in improving sleep study variables and sleepiness, and to evaluate compliance. A total of 3 prospective cohort studies and 4 RCTs were included in this review. Combined data for studies reporting on the effect of PT showed that there was a mean difference of 11.3 events/hour (54 % reduction) in AHI and 33.6 % (84 % reduction) in percentage total sleeping time in the supine position. The SMDs for both parameters demonstrated a large magnitude of effect (greater than 0.8 in both cases). The authors concluded that there is strong evidence that the new generation of devices for PT were

effective in reducing the AHI during short-term follow-up. These devices were simple-to-use for patients and clinicians and were reversible. Under study conditions with short-term follow-up, compliance was high; however, long-term compliance could not be evaluated because of lack of reliable data. These researchers stated that additional long-term, high-quality studies are needed to confirm the promising role of PT as a single or as a combination treatment modality for OSA patients and to assess long-term compliance.

In a multi-center, cohort study, Benoist and colleagues (2019) examined the effect of a SPT in patients with positional central sleep apnea (PCSA). Patients with symptomatic PCSA were included. Effectiveness, compliance and QOL were assessed at 1- and 6-month follow-up. A total of 16 patients were included. Median AHI dropped from 23.4/hour [12.9 to 31.2] to 11.5/hour [7.2 to 24.5] ($p = 0.044$) after 1-month SPT therapy and in patients who continued treatment, median AHI further decreased after 6 months to 9.7/hour [3.4 to 27.6] ($p = 0.075$). Median percentage of supine sleep decreased significantly from 37.6 [17.2 to 51.8] to 6.7 [0.7 to 22.8] ($p < 0.001$), after 1 month, and to 6.8 [0.7 to 22.1] ($p = 0.001$), after 6 months. Mean compliance over 1 and 6 months was 78.6 ± 35.3 and 66.0 ± 33.3 %, respectively; ESS at baseline was 9.5 [3.3 to 11.8] and did not significantly decrease after 1 month (11.0 [3.0 to 13.0]) and 6 months (4.0 [3.0 to 10.5]) follow-up. Functional Outcomes of Sleep Questionnaire remained stable within the 1st month. However, after 6 months, there was a significant improvement compared to baseline values (15.9 [11.9 to 18.4] versus 17.8 [14.3 to 19.2]; $p = 0.030$). The authors concluded that this was the first study on effects of PT with a new-generation smart device in patients with PCSA after 1 and 6 months of follow-up. Results of this study showed that the SPT was effective in reducing AHI and central AI, feasible in PCSA, and was associated with symptomatic improvement. While the working mechanism behind this effect remains speculative, the effect is positive and considerable. This was a small ($n = 16$) study with mid-term follow-up (6 months); its findings need to be validated by well-designed studies.

Srijithesh and co-workers (2019) noted that the modalities of therapy for OSA include behavioral and lifestyle modifications, PT, oral appliances, surgery and CPAP therapy. Although CPAP has proven efficacy in treating OSA, adherence with CPAP therapy is sub-optimal. Positional therapy is less invasive and thus expected to have better adherence. In a Cochrane review, these researchers examined the efficacy of PT compared to CPAP as well as PT against no PT.

Devices designed for PT include lumbar or abdominal binders, semi-rigid backpacks, full-length pillows, a tennis ball attached to the back of nightwear, and electrical sensors with alarms that indicate change in position. These investigators compared the efficacy of PT versus CPAP and PT versus inactive control (sham intervention or no PT intervention) in people with OSA. They identified studies from the Cochrane Airways' Specialized Register (including CENTRAL, Medline, Embase, CINAHL, AHMED and PsycINFO), ClinicalTrials.gov, and the World Health Organization trials portal (ICTRP). It also contained results derived from hand-searching of respiratory journals and abstract books of major annual meetings. They searched all databases from their inception to September 2018, with no restrictions on language of publication or publication type; RCTs comparing PT with CPAP and PT with inactive control were included. Two review authors independently selected studies and extracted the data. They used a random-effects model in the meta-analysis to estimate MDs and CIs; and assessed certainty of evidence using the GRADE approach. A total of 8 studies were included. The studies randomized 323 participants into 2 types of interventions. The comparison between PT and CPAP included 72 participants, while the comparison between PT and inactive control included 251 participants; 3 studies used supine vibration alarm devices, while 5 studies used physical positioning like specially designed pillows or semi-rigid backpacks. Positional therapy versus CPAP -- The 3 studies included for this comparison were randomized cross-over trials; 2 studies found that there was no difference in Epworth Sleepiness Scale (ESS) scores between CPAP and PT; 2 studies showed that CPAP produced a greater reduction in AHI with a MD of 6.4 events per hour (95 % CI: 3.00 to 9.79; low-certainty evidence) compared to PT. Subjective adherence, evaluated in 1 study, was found to be significantly greater with PT (MD 2.5 hours/night, 95 % CI: 1.41 to 3.59; moderate-certainty evidence). In terms of secondary outcomes, 1 study each reported QOL indices and quality-of-sleep indices with no significant difference between the 2 groups. One study reported cognitive outcomes using multiple parameters and found no difference between the groups. There were insufficient data to comment on other secondary outcomes like RDI, and frequency and duration of nocturnal desaturation. None of the studies clearly reported adverse effects. Positional therapy versus inactive control – A total of 3 studies of PT versus no intervention were randomized cross-over trials, while 2 studies were parallel-arm studies. Data from 2 studies showed that PT significantly improved ESS scores (MD -1.58, 95 % CI: -2.89 to -0.29; moderate-certainty evidence). Positional therapy showed a reduction in AHI compared with control (MD -7.38 events/hour, 95 % CI: -10.06 to -4.7; low-certainty evidence). One study reported

adherence. The number of participants who continued to use the device at 2 months was no different between the 2 groups (OR 0.80, 95 % CI: 0.33 to 1.94; low-certainty evidence). The same study reported adverse effects, the most common being pain in the back and chest, and sleep disturbance but there was no significant difference between the 2 groups in terms of device discontinuation (OR 1.25, 95 % CI: 0.5 to 3.03; low-certainty evidence). One study each reported QOL indices and quality-of-sleep indices, with no significant difference between the 2 groups.

One study reported cognitive outcome, and found no difference between the groups. There was insufficient evidence to comment on other secondary outcomes (RDI, frequency and duration of nocturnal desaturation). The authors concluded that this review found that CPAP had a greater effect on improving AHI compared with PT in positional OSA, while PT was better than inactive control for improving ESS and AHI. Positional therapy may have better adherence than CPAP. There were no significant differences for other clinically relevant outcomes such as QOL or cognitive function. All the studies were of short duration. These researchers stated that they were unable to comment on the long-term effects of the therapies. This is important, as most of the QOL outcomes will be evident only when the therapies are given over a longer period of time.

The certainty of evidence was low-to-moderate.

The Lunoa System, a sleep position therapy device, was cleared by the FDA via the 510k process in June 2018. It is indicated for the treatment of adult patients with positional OSA with a non-supine AHI of less than 20. It records position and movement so that positional changes in sleep quality can be assessed. The Lunoa system has 3 components operated as 1 system to provide treatment for POSA. It has a sensor, chest strap, docking station, power adapter, travel case, and portal. The sensor is battery-operated, re-chargeable, worn around the chest. The sensor contains a digital accelerometer that continually monitors a patient's sleep position. By emitting the vibro-tactile feedback during sleep, the sensor has been proven to keep patients with POSA from sleeping in the supine position. When using the device, if the patient turns to a supine position, the device vibrates until the patient moves to a non-supine position. However, there is insufficient evidence regarding the effectiveness of this device.

Respiratory Muscle Therapy

In a systematic review and meta-analysis, Hsu and colleagues (2020) examined the effects of respiratory muscle therapy (i.e., breathing exercises, oropharyngeal exercises, speech therapy, and wind musical instruments) compared to control therapy or no treatment in improving AHI (primary outcome), sleepiness and other polysomnographic outcomes for patients diagnosed with OSA. Only RCTs with a placebo therapy or no treatment searched using PubMed, Embase, Cochrane and Web of Science up to November 2018 were included and assessment of risk of bias was completed using the Cochrane handbook. A total of 9 studies with 394 adults and children diagnosed with mild-to-severe OSA were included, all assessed at high risk of bias; 8 of the 9 studies measured AHI and showed a weighted average overall AHI improvement of 39.5 % versus baselines following respiratory muscle therapy. Based on the meta-analyses in adult studies, respiratory muscle therapy yielded an improvement in AHI of -7.6 events/hour (95 % [CI: -11.7 to -3.5; $p \leq 0.001$]), apnea index of -4.2 events/hour (95 % CI: -7.7 to -0.8; $p \leq 0.016$), ESS of -2.5 out of 24 (95 % CI: -5.1 to -0.1; $p \leq 0.066$), PSQI of -1.3 out of 21 (95 % CI: -2.4 to -0.2; $p \leq 0.026$), snoring frequency ($p = 0.044$) in intervention groups compared to controls. The authors concluded that the findings of this systematic review highlighted respiratory muscle therapy as an adjunct management for OSA; however, further studies are needed, due to limitations including the nature and small number of studies, heterogeneity of the interventions and high risk of bias with low quality of evidence.

Measurements of Plasma and Serum Interleukin-6 Levels

Imani and colleagues (2020a) noted that OSAS is considered a low-grade chronic inflammatory disease. Interleukin-6 (IL-6) is one of the most significant inflammatory markers and an excellent proxy for the inflammatory/immune system. In a meta-analysis and meta-regression, these researchers compared plasma and serum levels of IL-6 between individuals (children and adults) with OSAS and healthy controls. A total of 4 data-bases (PubMed/Medline, Scopus, Cochrane Library, and Web of Science) were searched to retrieve articles published up to December, 2019, with no further restrictions. RevMan 5.3 software was used to calculate the crude mean difference (MD) and 95 % CI. The results of funnel plots and meta-regression were analyzed by the CMA 2.0 software. A total of 63 studies (57 with adults; 6 with children) were included in the present meta-analysis. For adults, 37 studies reported significantly higher serum IL-6 levels and

20 reported significantly higher plasma IL-6 levels for those with OSAS than for healthy controls [pooled MD of 2.89 pg/ml ($p < 0.00001$) and pooled MD of 2.89 pg/ml ($p < 0.00001$), respectively]. The pooled analysis of serum and plasma IL-6 levels in children with OSAS compared with controls revealed that only the MD of plasma IL-6 levels was significant (MD = 0.84 pg/ml, $p = 0.004$). Results of the meta-regression showed that greater age was associated with higher serum IL-6 levels. Egger's test revealed a publication bias across the studies for serum and plasma IL-6 levels ($p = 0.00044$, and $p = 0.01445$, respectively). The authors concluded that the meta-analysis and meta-regression confirmed that, compared to healthy controls, individuals with OSAS (children and adults) had higher serum/plasma IL-6 levels. Moreover, these researchers stated that future studies might examine the extent to which interventions to address OSAS (e.g., using CPAP devices) impact positively on IL-6 levels and possibly also on weight regulation.

The authors stated that this meta-analysis had several drawbacks. First, in none of the studies was results adjusted to reflect possible confounding factors such as obesity, smoking, or alcohol consumption. Second, the results of the funnel plots showed a publication bias across the studies; it followed that a systematic bias in data presentation could not be ruled out. Third, the studies with small sample sizes (less than 100) had insufficient power to detect associations. Fourth, there was a high level of heterogeneity among studies with respect to some analyses. Fifth, studies reported different cut-off values for AHI, making comparisons between the studies difficult. Sixth, in some studies, level of IL-6 was treated as a secondary outcome.

Measurements of Plasma and Serum Tumor Necrosis Factor Alpha Levels

Imani and associates (2020b) stated that OSAS is associated with a variety of inflammatory factors. Specifically, pro-inflammatory cytokines appeared to be associated with the pathogenesis of OSAS. For the present meta-analysis and meta-regression on serum and plasma tumor necrosis factor alpha (TNF- α) levels in individuals with and without OSAS, these researchers carried out a systematic search without any restrictions of the PubMed/Medline, Scopus, Cochrane Library, and Web of Science databases to identify relevant articles published up to February 1, 2020. A total of 55 (adults: 29 studies on serum and 17 studies on plasma; children: 4 studies on serum and 5 studies on plasma) were included and analyzed. Always compared to

age-matched healthy controls, the pooled MDs were as follows: adults, serum: 10.22 pg/ml (95% CI: 8.86 to 11.58; p < 0.00001); adults, plasma: 5.90 pg/ml (95 % CI: 4.00 to 7.80; p < 0.00001); children, serum: 0.21 pg/ml (95 % CI: 0.05 to 0.37; p = 0.01); children, plasma: 5.90 pg/ml (95 % CI: 4.00 to 7.80; p < 0.00001). The authors concluded that compared to healthy and age-matched controls, adult individuals with OSAS had significantly higher serum/plasma TNF- α levels. For children with OSAS, significantly higher levels were observed for TNF- α in serum but not in plasma. They noted that the findings of this meta-analysis showed that elevated TNF- α levels in individuals with OSAS appeared to be related to the severity of the disease. Moreover, these researchers stated that future studies should examine if and to what extent interventions on OSAS (e.g., using CPAP devices) favorably impact on TNF- α levels and possibly also on weight regulation.

The authors stated that this meta-analysis had several drawbacks. First, in all studies, results have not been adjusted for possible confounding factors such as obesity, smoking, or alcohol consumption. Second, the results of the funnel plots showed a publication bias across the studies; it followed that a systematic bias in the data presentation could not be ruled out. Third, studies with a small sample size (less than 100 cases) had an inadequate power to detect possibly meaningful associations. Fourth, there was a high heterogeneity among studies in some analyses. Fifth, studies reported different cut-off AHI values, which made comparisons between the studies difficult. Sixth, in some studies, TNF- α levels were considered as secondary outcome. Finally, in some studies, the existence of mixed ethnicities might have blurred the associations between the ethnicity and TNF- α levels.

Cao and colleagues (2020) noted that TNF- α has been reported to play a part in the development of OSA and its complications; however, the relationship between TNF- α and OSA still remains inconclusive. In a systematic review, these investigators examined studies published to-date on association between the two in adults. They searched for English-language articles containing original human data from case-control study studies in adults greater than or equal to 18 years of age. The selection criteria were set according to the PICOS framework. Articles were independently reviewed by 3 investigators. Data regarding demographics, clinical characteristics, and TNF- α levels were obtained. A random-effects model was employed to examine the overall effect sizes by calculating SMD and its 95 % CIs. Of 393 identified abstracts, 50 articles (3,503

OSA patients and 3,379 health controls) were included in this meta-analysis. The results indicated that the TNF- α level in patients with OSA was 1.77 (95 % CI: 1.37 to 2.17, $I^2 = 97.8 \%$, $p < 0.0001$) times higher than in the control group. Subgroup analyses showed a positive correlation between the level of TNF- α and OSA severity. According to meta-regression, these researchers noted that aging significantly predicted an increased effect size of TNF- α level in OSA patients ($p < 0.007$). The authors concluded that this study identified a significant association between OSA and elevated TNF- α level in adults; TNF- α levels were consistently correlated with severity of OSA, which indicated it might be a promising biomarker for the development of OSA. Moreover, these researchers stated that well-designed, large-scale, case-control cohorts are needed to better understand the relationship of TNF- α in the context of adult OSA.

Endoscopically-Assisted Surgical Expansion (EASE)

In a retrospective study, Li et al (2019) examined the results of an outpatient surgical procedure known as endoscopically-assisted surgical expansion (EASE) in expanding the maxilla to treat obstructive sleep apnea (OSA) in adolescent and adults. A total of 33 patients (18 males), aged 15 to 61 years, underwent EASE of the maxilla. All patients completed pre- and post-operative clinical evaluations, polysomnography (PSG), questionnaires (Epworth Sleepiness Scale [ESS] and Nasal Obstruction Septoplasty Questionnaire [NOSE]) as well as cone beam computed tomography (CBCT). With EASE, the overall apnea hypopnea index (AHI) improved from 31.6 ± 11.3 to 10.1 ± 6.3 . The oxygen desaturation index (ODI) improved from 11.8 ± 9.6 to 1.8 ± 3.7 , with reduction of ESS scores from 13.4 ± 4.0 to 6.7 ± 3.1 . Nasal breathing improved as demonstrated by reduction of the NOSE scores from 57.8 ± 12.9 to 15.6 ± 5.7 . Expansion of the airway from widening of the nasal floor was consistently evident on all post-operative CBCT; the anterior nasal floor expanded 4.9 ± 1.2 mm, posterior nasal floor expanded 5.6 ± 1.2 mm, and the dental diastema created was 2.3 ± 0.8 mm. Mean operative time was 54.0 ± 6.0 mins. All patients with mild-to-moderate OSA were discharged the same day; patients with severe OSA were observed overnight. All patients returned to school or work and regular activities within 3 days. The authors concluded that EASE was an outpatient procedure that improved nasal breathing and OSA by widening the nasal floor in adolescents and adults. Compared to current surgical approaches for maxillary expansion, EASE is considerably less invasive and consistently

achieves enlargement of the airway with minimal complications. One of the keywords listed in this study was SARPE. This was a small ($n = 33$), retrospective study; its findings need to be validated by well-designed studies.

Furthermore, an UpToDate review on “Surgical treatment of obstructive sleep apnea in adults” (Weaver and Kapur, 2021) does not mention endoscopically-assisted surgical expansion (EASE) as a management / therapeutic option.

Surgical Palatal Expansion

Hur et al (2017) examined the effects of miniscrew-assisted rapid palatal expansion (MARPE) on changes in airflow in the upper airway (UA) of an adult patient with OSA syndrome (OSAS) using computational fluid-structure interaction analysis. Three-dimensional (3D) UA models fabricated from cone beam computed tomography (CBCT) images obtained before (T0) and after (T1) MARPE in an adult patient with OSAS were used for computational fluid dynamics with fluid-structure interaction analysis; 7 and 9 cross-sectional planes (interplane distance of 10 mm) in the nasal cavity (NC) and pharynx, respectively, were set along UA. Changes in the cross-sectional area (CSA) and changes in airflow velocity and pressure, node displacement, and total resistance at maximum inspiration (MI), rest, and maximum expiration (ME) were examined at each plane after MARPE. The CSAs at most planes in NC and the upper half of the pharynx were significantly increased at T1. Moreover, airflow velocity decreased in the anterior NC at MI and ME and in the nasopharynx and oropharynx at MI. The decrease in velocity was greater in NC than in the pharynx. The airflow pressure in the anterior NC and entire pharynx exhibited a decrease at T1. The amount of node displacement in NC and the pharynx was insignificant at both T0 and T1. Absolute values for the total resistance at MI, rest, and ME were lower at T1 than at T0. The authors concluded that MARPE improved airflow and decreased resistance in UA; thus, it may be an effective treatment modality for adult patients with moderate OSAS.

Furthermore, an UpToDate review on “Surgical treatment of obstructive sleep apnea in adults” (Weaver and Kapur, 2021) does not mention palatal expansion as a management / therapeutic option.

Transcutaneous Electrical Nerve Stimulation (TENS)

In a systematic review and meta-analysis, Byun and colleagues (2020) examined the treatment efficacy of transcutaneous electrical nerve stimulation (TENS) in patients with OSA. Primary studies were identified through PubMed, Scopus, OVID, and Cochrane Library. These researchers carried out a systematic review by examining data-bases for articles published through July 2019. The search identified RCT, randomized comparison, or observational studies pertaining to TENS treatment for OSA. Meta-analysis was carried out on pre- and post-treatment AHI, mean SaO₂, LSAT, and arousal index (AI). The search identified 10 studies that reported sufficient outcome measures to be considered for analysis. A total of 198 patients were identified with a mean age of 50.9 years with a male:female ratio of 1.6:1. Average BMI of the cohort was 29.8 kg/m². Treatment with TENS demonstrated reduction in AHI by 12.9 points (95 % CI: -22.3 to -3.43; p = 0.008). The mean differences in SaO₂, LSAT, and AI did not reach statistical significance. The authors concluded that TENS treatment of upper airway dilator muscles resulted in reduction of AHI in patients with OSA. However, its effects on SaO₂, LSAT, and AI were equivocal. Its impact on patients' QOL could not be assessed due to heterogeneity in outcome measures. These researchers stated that future RCTs with generalizable standardized outcome measures are needed to examine the compliance and effectiveness of TENS.

Ratneswaran and associates (2021) stated that electrical stimulation (ES) of the upper airway dilator muscles is an emerging treatment for OSA. Invasive HNS has been accepted as treatment alternative to CPAP for selected patients, while transcutaneous ES (TES) of the upper airway is being examined as non-invasive alternative. These investigators carried out a meta-analysis on the effects of both HNS and TES on AHI and the ESS in OSA including published evidence up to May 2018; random-effects models were used. Heterogeneity and between-study variance were assessed by I² and τ², respectively. Of the 41 identified clinical trials, 20 interventional trials (n = 895) could be pooled in a meta-analysis (15 HNS [n = 808], 5 TES [n = 87]). Middle-aged (mean ± SD 56.9 ± 5.5 years) and over-weight (BMI of 29.1 ± 1.5 kg/m²) patients with severe OSA (AHI 37.5 ± 7.0/h) were followed-up for 6.9 ± 4.0 months (HNS) and 0.2 ± 0.4 months (TES), respectively. The AHI improved by - 24.9/hour [95 % CI: - 28.5 to - 21.2] in HNS ($\chi^2 = 79$ %, I² = 82 %) and by - 16.5/hour [95 % CI: - 25.1 to - 7.8] in TES ($\chi^2 = 7$ %, I² = 43 %; both p < 0.001). The ESS was reduced by - 5.0 (95 % CI: - 5.9 to - 4.1) (p < 0.001). The authors concluded that

both invasive and transcutaneous ES reduced OSA severity by a clinically relevant margin; HNS resulted in a clinically relevant improvement of symptoms. These researchers stated that while HNS represents an invasive treatment for selected patients with moderate-to-severe OSA, TES should be further examined as potential non-invasive approach for OSA.

Slow Wave DS8

Slow Wave DS8 is a mandibular re-positioning device designed to reduce or alleviate snoring and mild-to-moderate OSA in adults. DS8 consists of 2 custom fitted trays used to reposition the mandible. The trays are designed to be worn on the upper and lower teeth where they act to increase users' pharyngeal space by reducing obstructions of the airway during sleep; thus, improving their ability to exchange air during sleep. The device is designed to be retained on the teeth with saliva and surface tension and functions without any screws or fastening mechanism. The patient-custom devices are 3D print manufactured and made from biocompatible material.

There is a lack of evidence regarding the effectiveness of the Slow Wave DS8 in reducing or alleviating snoring.

Circulating Malondialdehyde Concentrations as a Biomarker for OSA

Pau and colleagues (2021) noted that oxidative stress induced by nocturnal intermittent hypoxia plays a significant pathophysiological role in OSA. Malondialdehyde (MDA), one of the most commonly investigated markers of lipid peroxidation, might aid in monitoring of oxidative balance in OSA. In a systematic review and meta-analysis, these researchers examined the differences in circulating MDA concentrations between patients with OSA and non-OSA controls. They carried out a systematic search in the electronic databases PubMed, Web of Science, Scopus and Google Scholar from inception to December 2020 by using the following terms:

"malondialdehyde" or "MDA"; and "Obstructive Sleep Apnea Syndrome", "OSAS" or "OSA". They identified 26 studies in 1,223 OSA patients and 716 controls. The pooled MDA concentrations were significantly higher in patients with OSA (SMD 1.43 $\mu\text{mol/L}$, 95 % CI: 1.03 to 1.83 $\mu\text{mol/L}$, $p < 0.001$). There was extreme heterogeneity between the studies ($I^2 = 92.3 \%$, $p < 0.001$). In meta-regression analysis, the SMD was significantly associated with age, the assay type used and publication year. The authors concluded that in this meta-analysis the significantly higher

MDA concentrations observed in OSA patients, when compared to non-OSA subjects, supported the presence of lipid peroxidation in OSA. The significant heterogeneity observed warrants the use of standardized methods and adequate definitions of non-OSA subjects in future studies examining the possible use of MDA as a clinical biomarker of OSA and to monitor the effects of interventions.

These researchers stated that in the evaluation of the relationship between effect size and disease severity, the pooled SMD showed that MDA concentrations were significantly higher in patients with severe OSA compared to those with mild OSA. Although the number of studies that analyzed OSA patients according to the AHI was limited, these findings suggested the presence of a relation between severity of disease and oxidative stress. The analysis of the effect of OSA treatment on circulating MDA concentrations, especially in relation with different degrees of severity, represents an important issue. However, the lack of RCTs reporting this feature represents another limitation of this trial. Nevertheless, this meta-analysis provided robust background information for the adequate design and conduct of further studies addressing this issue, especially the usefulness of this marker for monitoring OSA and the effects of therapies. A recent meta-analysis has already demonstrated an increase of MDA in patients with OSA compared to the controls. Even though the data obtained in terms of pooled SMD were similar in the 2 meta-analyses, this systematic search retrieved 26 studies involving a higher number of subjects compared to 14 studies analyzed by Fadaei et al (2021). Furthermore, the largest number of included articles allowed more factors relative to the investigation that might be related to the pooled SMD; these factors included publication year, geographic area, lipid profile and type of biological sample. Finally, this trial also analyzed the concentrations of MDA in relation to disease severity; thus, this study provided a more detailed picture with respect to MDA levels in OSA patients.

Contraction of the Sternothyroid Muscle with Ansa Cervicalis Stimulation for the Treatment of OSA

Kent and colleagues (2021) noted that HNS is an alternative therapeutic option for patients with OSA unable to tolerate PAP; however, implant criteria limit treatment candidacy. Previous research indicated that caudal tracheal traction plays an important role in stabilizing upper airway

patency. These researchers examined if contraction of the sternothyroid muscle with ansa cervicalis stimulation (ACS), which pulls the pharynx caudally via thyroid cartilage insertions, increase maximum inspiratory airflow (V_Imax). Hook-wire percutaneous electrodes were used to stimulate the medial branch of the right hypoglossal nerve and right branch of the ansa cervicalis innervating the sternothyroid muscle during propofol sedation. V_Imax was evaluated during flow-limited inspiration with a pneumotachometer. A total of 8 subjects with OSA were studied using ACS with and without HNS. Compared with baseline, the mean V_Imax increase with isolated ACS was 298 %, or 473 ml/s (95 % CI: 407 to 539). Isolated HNS increased mean V_Imax from baseline by 285 %, or 260 ml/s (95 % CI: 216 to 303). Adding ACS to HNS during flow-limited inspiration increased mean V_Imax by 151 %, or 205 ml/s (95 % CI: 174 to 236) over isolated HNS. Stimulation was significantly associated with increase in V_Imax in both experiments ($p < 0.001$). The authors concluded that ACS independently increased V_Imax during propofol sedation and drove further increases in V_Imax when combined with HNS. The branch of the ansa cervicalis innervating the sternothyroid muscle was easily accessed. These researchers stated that confirmation of the ansa cervicalis as a viable neurostimulation target may enable caudal pharyngeal traction as a novel respiratory neurostimulation strategy for the treatment of OSA.

Dynamic Sleep MRI for the Diagnosis of OSA

In a systematic review and meta-analysis, Volner and colleagues (2022) examined the available evidence for dynamic sleep MRI as a diagnostic tool for OSA. These researchers carried out a comprehensive review of the literature, followed by a detailed analysis of the relevant data that has been published on the topic. Clinical key, UpToDate, Ovid, Ebscohost, PubMed/Medline, Scopus, Dynamed, Web of Science and the Cochrane Library were systematically searched. Once the search was completed, dynamic sleep MRI data were analyzed. A total of 19 articles reported on 410 OSA patients and 79 controls who underwent dynamic sleep MRI and were included in this review. For meta-analysis of dynamic sleep MRI data, 8 articles presented relevant data on 160 OSA patients. Obstruction was reported as follows: retropalatal (RP) 98 %, retroglossal (RG) 41 % and hypopharyngeal (HP) in 5 %. Lateral pharyngeal wall (LPW) collapse was found in 35/73 (48 %) patients. The combinations of RP + RG were observed in 24 % and RP + RG + LPW in 16 %. If sedation was used, 98 % of study participants fell asleep compared to 66 % of un-sedated participants. The authors concluded that dynamic sleep MRI is an exciting

adjunct for the evaluation of OSA patients and determining the specific locations and patterns of obstruction. This study corroborated the finding that RP collapse is the most prevalent finding in males with severe OSA. Dynamic sleep MRI could be performed under natural sleep, although there is a higher efficacy with various sedation methods. For control groups in future studies, it is imperative to include BMI-matched non-OSA patients. Furthermore, measurement of airway obstructions in a standardized approach with standardized nomenclature of the levels of obstruction (nasopharyngeal [NP], RP, RG, HP, and LPW) will allow correlation between observances. Along with sagittal images, axial and coronal images would need to be employed to determine more precise patterns of collapse and especially elucidate the extent of LPW collapse. These researchers stated that, potentially, if able to overcome these challenges, dynamic sleep MRI could be used to a broader clinical practice to guide appropriate surgical decision-making for severe OSA patient with multi-level collapse or refractory to initial surgical intervention.

Measurement of Blood Levels of C-Reactive Protein and Development of OSA

Huang and colleagues (2021) noted that individuals with OSA have increased levels of inflammatory markers; however, no prospective study has examined the role of inflammation in the development of OSA. These researchers examined if C-reactive protein (CRP) is associated with risk of developing OSA. They followed 1,882 women from the Nurses' Health Study (NHS) (2002 to 2012), 3,854 women from Nurses' Health Study II (NHSII) (1995 to 2013), 3,075 men from the Health Professionals Follow-up Study (HPFS) (1996 to 2012), and 1,919 women and men from the Multi-Ethnic Study of Atherosclerosis (MESA) (2000 to 2012) who did not have diagnosed OSA at baseline and for whom CRP levels were available. In NHS/NHSII/HPFS, physician-diagnosed OSA was self-reported. In MESA, at-home PSG was carried out and OSA was identified as an AHI of greater than or equal to 30. Logistic regression was used to estimate the OR for OSA risk according to baseline CRP level, adjusted for multiple inflammation-related factors. After multi-variable adjustment not including BMI, the pooled OR for OSA risk per doubling of baseline CRP level was 1.24 (95 % CI: 1.18 to 1.30). Additional adjustment for BMI substantially attenuated the association (pooled OR, 1.07; 95 % CI: 1.01 to 1.12). The fully adjusted association was consistently stronger in individuals less than 55 versus greater than or equal to 55 years of age (p interaction = 0.01), in individuals with BMI less than 25 versus greater than or equal to 25 kg/m² (p interaction = 0.02), and in pre- versus post-menopausal women (p

interaction = 0.002). CRP was more strongly associated with risk of OSA associated with excessive daytime sleepiness, high airway collapsibility, and low arousal threshold (p heterogeneity < 0.05). The authors concluded that higher CRP was prospectively associated with increased OSA risk, especially among younger individuals, under-weight/normal-weight individuals, or pre-menopausal women. The differential associations by OSA phenotype/endotype suggested possible mechanisms through which inflammation operates to modulate OSA risk.

These researchers stated that given the reliance on a single CRP level measured a decade before OSA assessment, future studies with repeated CRP measurements are needed to confirm these prospective associations.

Imani and associates (2021) stated that high sensitivity CRP (hs-CRP) and CRP are inflammatory biomarkers associated with several inflammatory diseases. In both pediatric and adult individuals with OSA, higher hs-CRP and CRP were observed, compared to controls. In a systematic review, meta-analysis and meta-regression, these researchers expanded upon previous meta-analyses in 4 ways: First, they included 109 studies (96 in adults and 13 in children). Second, they reported subgroup and meta-regression analyses in adults with OSA compared to controls on the serum and plasma levels of hs-CRP. Third, they reported subgroup and meta-regression analyses in adults with OSA compared to controls on the serum and plasma levels of CRP. Fourth, they reported serum and plasma levels of both hs-CRP and CRP in children with OSA, always compared to controls. The PubMed/Medline, Scopus, Cochrane Library, and Web of Science databases were searched to retrieve articles published until May 31, 2020, with no restrictions.

The data included basic information involving the first author, publication year, country of study, ethnicity of participants in each study, age, BMI, and AHI of both groups, and mean and standard deviation (SD) of plasma and serum levels of CRP and hs-CRP. A total of 1,046 records were retrieved from the databases, and 109 studies were selected for the analysis (96 studies reporting the blood levels of hs-CRP/CRP in adults and 13 studies in children). For adults, 11 studies reported plasma hs-CRP, 44 serum hs-CRP, 9 plasma CRP, and 32 serum CRP levels. For children, 6 studies reported plasma hs-CRP, 4 serum hs-CRP, 1 plasma CRP, and 2 serum CRP levels. Compared to controls, the pooled MD of plasma hs-CRP levels in adults with OSA was 0.11 mg/dL (p < 0.00001). Compared to controls, the pooled MD of serum hs-CRP levels in adults with OSA was 0.09 mg/dL (p < 0.00001). Compared to controls, the pooled MD of plasma CRP levels in adults with OSA was 0.06 mg/dL (p = 0.72). Compared to controls, the pooled MD

of serum CRP levels in adults with OSA was 0.36 mg/dL ($p < 0.00001$). Compared to controls, the pooled MD of plasma hs-CRP, serum hs-CRP, plasma hs-CRP, and serum hs-CRP in children with OSA was 1.17 mg/dL ($p = 0.005$), 0.18 mg/dL ($p = 0.05$), 0.08 mg/dL ($p = 0.10$), and 0.04 mg/dL ($p = 0.33$), respectively. The meta-regression showed that with a greater AHI, serum hs-CRP levels were significantly higher. The authors concluded that the findings of this systematic review, meta-analysis and meta-regression demonstrated that higher plasma and serum levels of hs-CRP and serum levels of CRP in individuals with OSA appeared to be associated with the disease severity. Further, higher AHI appeared to impact on the associations between OSA and CRP/hs-CRP levels. These researchers stated that future studies might consider, if and to what extent interventions on OSA (e.g., using CPAP devices) may favorably impact on CRP/hs-CRP levels and possibly also on weight regulation. While it appeared that the use of CPAP did not change the level of inflammatory markers after 12 weeks among women with OSA, it would be of clinical and practical importance to know if changes in hs-CRP and CRP would be associated with weight loss among individuals with OSA.

The authors stated that the novelty of the results should be balanced against the following drawbacks. First, in all studies the results were not adjusted based on possible confounding factors such as obesity, smoking, and alcohol consumption, and even in some studies based on gender. Second, there was a high heterogeneity and also a bias between and across studies, all of which could impact on the reliability of the results. Third, studies with a small sample size (less than 100) might have had insufficient power to detect associations between OSA, CRP and hs-CRP levels. Fourth, studies reported various cut-off AHI values, which made it difficult to compare the study results. Fifth, in some studies, CRP and hs-CRP levels were considered as a secondary outcome.

Measurement of Blood Levels of Interleukin-8 and Development of OSA Syndrome

Li and colleagues (2021) noted that interleukin (IL)-8 has been shown to play an important role in OSAS; however, its role in OSAS development is still controversial. In a meta-analysis, these researchers examined the correlation between IL-8 concentration and OSAS. Database (from the inception to July 2021) searches on PubMed, Web of Science, Medline, EMBASE, and Cochrane Library were conducted for studies analyzing the correlation between IL-8 concentration and

OSAS, regardless of the language of publication; SMD and 95 % CIs were used to analyze any prospective association between IL-8 concentration and OSAS. A total of 25 eligible studies, including 2,301 participants and 1,123 controls, were included in this meta-analysis. The included studies evaluating the association between serum IL-8 concentration and OSAS indicated that adults and children with OSAS had elevated serum concentrations of IL-8 compared with controls (SMD = 0.997, 95 % CI: 0.437 to 1.517, p < 0.001; SMD = 0.431, 95 % CI: 0.104 to 0.759, p = 0.01). Categorization of the study population into subgroups according to BMI, AHI, ethnicity, and sample size also showed that individuals with OSAS had elevated serum concentrations of IL-8 compared with controls. Furthermore, the results demonstrated that higher the AHI, higher was the IL-8 concentration. Similar results were observed in the literature on the association between plasma IL-8 concentration and OSAS. The authors concluded that this meta-analysis verified that compared with controls, children and adults with OSAS have significantly elevated IL-8 concentrations. Moreover, these researchers stated that future studies should be focused on OSAS interventions (e.g., use of CPAP devices) for the investigation of IL-8 concentrations and immune function.

The authors stated that although the findings of this meta-analysis were novel, the following drawbacks should be considered. First, the findings of the included studies did not suggest that adjustments were made for prospective confounding factors (e.g., obesity, smoking, staying up late, sex, or drinking). Second, the results of the included studies with a small sample size (less than 100) were not reliable as low statistical power led to a higher variability; thus, the relationship between IL-8 concentration and OSAS could not be considered to be adequately justified. Furthermore, only a few studies entailed the analysis of samples other than serum or plasma. Third, there was a high degree of heterogeneity between studies in some analyses. Meta-regression analysis showed that ethnicity, age, BMI, AHI, and sample size had little effect on heterogeneity. These researchers could not identify the source of the obvious heterogeneity, which may be related to experimental conditions, test reagents, physical differences in participants, and other confounding factors, all of which may affect the reliability of these findings. Fourth, IL-8 concentrations were considered secondary results in some studies; therefore, the evidence of support on the effect of IL-8 in OSAS might be low. Some of the studies suffered from significant sources of bias and this should be also taken into consideration.

Measurement of Blood Levels of Leptin and Development of OSA Syndrome

Li and He (2021) stated that OSAS is associated with various adipokines. Leptin, a common adipokine, has attracted considerable attention of many researchers in recent years. So far, there has been little agreement on whether blood leptin levels differ in patients with OSAS. In a meta-analysis, these researchers examined the relationship between serum/plasma leptin levels and the occurrence of OSAS. WanFang, Embase, CNKI, Medline, SinoMed, Web of Science, and PubMed were searched for articles before March 30, 2021, with no language limitations. STATA version 11.0 and R software version 3.6.1 were used to analyze the obtained data. The WMD and CIs were used as the main effect sizes with a random-effects model and a fixed-effects model, respectively. Trial sequential analysis was conducted using dedicated software.

Screening of 34 publications identified 45 studies that met the inclusion criteria of this meta-analysis and meta-regression. The results suggested that plasma/serum leptin levels were remarkably higher in individuals with OSAS than in healthy individuals. Subgroup analyses were carried out based on OSAS severity, ethnicity, age, BMI, assay type, and sample source. The serum and plasma leptin levels were increased in nearly all OSAS subgroups compared to those in the corresponding control groups. Meta-regression analysis indicated that age, BMI, severity, assay approaches, study design, PSG type and ethnicity did not have independent effect on leptin levels. Furthermore, a positive relationship between the serum/plasma leptin level and AHI was found in the meta-analysis. The results of the trial sequential analysis suggested that the enrolled studies surpassed the required information size, confirming that the findings of this study were reliable. The authors concluded that a high plasma leptin level may be correlated with OSA, and the serum/plasma leptin level positively correlated with AHI. Furthermore, ethnicity has an impact on the association between OSAS and leptin levels. Moreover, these researchers stated that more elaborate studies are needed to examine the association between leptin levels and OSAS risk.

The authors stated that despite the novelty of these findings, the following drawbacks should be considered. First, none of the studies was adjusted to reflect possible confounding factors such as stable daily routine, smoking, or alcohol consumption. And there were only 2 articles in the original literatures that concerned on male patients with OSA. Although these investigators tried their best to control the confound founding factors, some potential confounding factors may affect

the conclusion more or less. Second, since this study lacked effective longitudinal cohort studies, these researchers could not infer causality of the association between plasma/serum leptin levels and OSA. Third, the majority of the included studies had a sample size of fewer than 100 cases, which had insufficient power to analyze the association between leptin levels and OSAS.

Natural Sleep Endoscopy

In a systematic review, Van den Bossche and colleagues (2021) examined the literature on natural sleep endoscopy (NSE), including the set-up, different scoring systems, visualized collapse patterns during natural sleep, additional measurements, and comparison of upper airway collapse between NSE and drug-induced sleep endoscopy (DISE). A computerized search on Medline, Web of Science and the Cochrane library was conducted, obtaining 39 hits. A total of 10 prospective studies were included in which NSE was performed in adults with OSA. This study's findings suggested the soft palate to be the most frequent site of obstruction (58.8 %), followed by the tongue base (43.2 %), lateral walls (29.9 %), and epiglottis (22.4 %), which is in line with previous findings during DISE. Based on this literature review, the authors concluded that at this stage high quality, comparative research between DISE and NSE is missing. To adequately compare findings between OSA patients, endoscopic classification of upper airway collapse should be standardized. Non-invasive predictive tools to determine pharyngeal collapse are currently under investigation and may obviate the need for invasive endoscopy. This review highlighted the contribution of NSE in validating such novel diagnostic methods and in studying upper airway mechanics in a research setting, yet the literature on natural sleep endoscopy (NSE), including the set-up, different scoring systems, visualized collapse patterns during natural sleep, additional measurements, and comparison of upper airway collapse between NSE and drug-induced sleep endoscopy (DISE). A computerized search on Medline, Web of Science and the Cochrane library was conducted, obtaining 39 hits. Ten prospective studies were included in which NSE was performed in adults with obstructive sleep apnea (OSA). This study's findings suggest the soft palate to be the most frequent site of obstruction (58.8 %), followed by the tongue base (43.2 %), lateral walls (29.9 %), and epiglottis (22.4 %), which is in line with previous findings during DISE. Based on this literature review, the authors conclude that at this stage high quality, comparative research between DISE and NSE is missing. To adequately compare findings between OSA patients, endoscopic classification of upper airway collapse should be

standardized. Non-invasive predictive tools to determine pharyngeal collapse are currently under investigation and may obviate the need for invasive endoscopy. This review highlights the contribution of NSE in validating such novel diagnostic methods and in studying upper airway mechanics in a research setting, yet larger and adequately powered studies are needed.

The authors stated that due to the invasiveness of NSE, there is a paucity of work in this field; thus, articles in this systematic review were selected widely. While this allowed for a broad overview of the existing methods and literature, the different aims and methodologies throughout the studies may have led to considerable heterogeneity in the data. The included studies encountered several drawbacks, such as the use of different inclusion criteria regarding OSA severity and the relatively small sample size. Future studies with larger sample size are needed. Since 1 or 2 researchers must be present during an NSE for the whole night and only 1 to 2 patients can be examined per night, it is a time-consuming and labor-intensive study. Moreover, in certain studies, it was not possible to perform NSE for more than 20 mins due to awakening of the patient. During DISE, changes in obstruction patterns are known to be time-dependent; thus, differences in examination duration might have affected the different endoscopic results. During endoscopy, the site of upper airway collapse may be observed. However, a recent paper in children suggested that the observed site of collapse during DISE does not always corresponds with the primary site of flow limitation (Garcia and Woodson, 2020; Yanagisawa-Minami et al, 2020). More research is needed on the correlation between the site of upper airway collapse during natural and drug-induced sleep and the actual site of flow limitation. It is important to be aware of the inherent limitations of endoscopy such as its subjective nature. Previous DISE studies suggested generally poor-to-good inter-observer agreement with a higher inter-rater consistency in experienced versus non-experienced ENT surgeons. It appeared reasonable to expect similar findings during NSE, although current data are lacking.

Daytime Neuromuscular Stimulation of the Tongue

In February 2021, the U.S. FDA authorized marketing clearance for the eXciteOSA device (Signifier Medical Technologies, LLC) for the treatment of patients 18 years of age or older who have mild obstructive sleep apnea (Apnea-Hypopnea Index (AHI) 5-15) and snoring. The eXciteOSA is a non-invasive, removable, daytime intraoral (tongue) neuromuscular stimulation

device that is used to strengthen the tongue muscles by delivering electrical muscle stimulation through a mouthpiece that sits around the tongue. The eXciteOSA mouthpiece has four electrodes, two located above the tongue and two located below the tongue. The device provides electrical muscle stimulation action in sessions that consist of a series of electrical pulses with rest periods in between. It is used for 20 minutes once a day during a wakeful state, for a period of 6-weeks, and once a week thereafter to reduce snoring and mild OSA. The eXciteOSA device can be controlled by a mobile smartphone application (FDA, 2021; Signifier Medical Technologies, 2021).

The FDA clearance was based on the safety and effectiveness of the eXciteOSA device (previously named Snoozeal) that was evaluated in 115 patients with snoring, including 48 patients with snoring and mild sleep apnea (AHI less than 15). All patients used the device for 20 minutes, once a day for 6 weeks, then discontinued use for 2 weeks before they were reassessed. Objective snoring and respiratory parameters were recorded with 2 consecutive WatchPAT night sleep studies before and after the use of the device. Overall, the percent of time spent snoring at levels louder than 40dB was reduced by more than 20% in 87 out of the 115 patients. In a 48-patient subset with snoring and mild OSA, the average AHI reduced by 48%, from 10.21 to 5.27, in 41 out of 48 patients. The most common adverse events observed were excessive salivation, tongue or tooth discomfort, tongue tingling, dental filling sensitivity, metallic taste, gagging and tight jaw (FDA, 2021).

Baptista et al (2021) conducted a multicenter prospective study to evaluate daytime neuromuscular electrical training (NMES) of tongue muscles in individuals with primary snoring and mild obstructive sleep apnea (OSA). Patients were included if they were 18 years of age or older, had a live-in partner to report on snoring, had a history of at least 6 months of habitual snoring of more than 5 days per week, and patients were confirmed to have an AHI less than 15 per the Watch-PAT 200 device. Patients were excluded if they had a BMI greater than 35 kg/m², symptomatic nasal pathology, tonsil hypertrophy (tonsil size of grade 3 or greater), tongue or lip piercing, pacemaker or implanted medical electrical devices, previous oral surgery for snoring, relevant facial skeletal abnormalities, or significant oral disease/conditions. Patients used the eXciteOSA device (Signifier Medical Technologies) for 20 minutes once daily for 6 weeks. Change in percentage time spent snoring was analyzed using a two-night sleep study before and

after therapy. Participants and their bed partners completed sleep quality questionnaires: Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI), and the bed partners reported on the nighttime snoring using a Visual Analogue Scale (VAS). Of 125 patients recruited, 115 patients completed the trial. Ninety percent of the study population had some reduction in objective snoring with the mean reduction in the study population of 41% ($p < 0.001$). Bed partner-reported snoring reduced significantly by 39% ($p < 0.001$). ESS and total PSQI scores reduced significantly ($p < 0.001$) as well as bed partner PSQI ($p = 0.017$). No serious adverse events were reported. The authors concluded that daytime NMES, using the eXciteOSA device, was demonstrated to be effective at reducing objective and subjective snoring, and was associated with improvement in sleep quality and daytime somnolence by the patient. Daytime NMES was well tolerated and had minimal transient side effects. Limitations of the study included need for a prospective randomized controlled trial. However, the authors state that “there are inherent challenges in designing a study of a device with an awake stage mode of action on one of the body’s primary sensory organs and presents challenges in creating appropriate blinding. Whilst it would be technically possible to provide users with a deactivated device that does not produce an electrical signal, it may be relatively easy for users to deduce if they are receiving sham or active therapy. Randomizing and conducting comparative analysis against [mandibular advancement devices] might be a more appropriate future trial design. Another limitation of this study was the limited duration of follow-up, a common issue with many early trials of emerging technologies. The official research statement by the American Thoracic society identified many gaps in the current literature related to mild OSA therapy options and makes recommendations on the research priorities and need for further studies. Further studies are planned to capture long-term outcomes and follow guidance set by the task force”. A Phase IV prospective, multicenter post-market surveillance study is in progress (NCT04392765).

Kotecha et al (2021) conducted a prospective cohort study to ascertain the usefulness of a novel intraoral neuromuscular stimulation device (eXciteOSA) in treating patients with primary snoring and mild obstructive sleep apnea (OSA). Patients were required to be 18 years of age or older, have been suffering from habitual snoring (more than 5 out of 7 nights per week) for more than 6 months, and have a live-in partner. Patients were excluded if they had a body mass index (BMI) greater than 35, AHI greater than 15, had symptomatic nasal pathology, tonsillar hypertrophy at grade 3 or above, had tongue piercing, pacemakers or implanted electrical medical devices.

Patients who had previous oral surgery for snoring and those with relevant facial skeletal abnormalities were also excluded. Out of 75 patients enrolled, 70 completed the study. Objective snoring and respiratory parameters were recorded with 2 consecutive night WatchPat sleep studies before and after treatment. The device was used for 20 minutes once daily for a 6-week period. Secondary outcome measures using visual analogue scale reporting of snoring by patient and Epworth Sleepiness Score (ESS) were recorded. Quality of life parameters were also noted. Objective reduction of snoring was noted on the sleep studies in 95% of participants, with an average snoring time reduction of 48%. Subjectively, the visual analogue scale reported by partners' similarly demonstrated reduction in 95% of the patients with an average reduction of 40%. In a subset of 38 patients with mild OSA, AHI reduced from 9.8 to 4.7/h (52% reduction), ODI 7.8 to 4.3/h (45% reduction), and ESS from 9.0 to 5.1. Adverse effects encountered were minimal. The authors concluded that this study demonstrates a notable improvement in both objective and subjective parameters of snoring and mild OSA in both simple snorers and patients with mild OSA. The authors state that this device offers a safe and novel approach to reduce snoring and mild OSA by utilizing intraoral neuromuscular electrical stimulation; however, further studies are planned to include 3- and 6-month follow-up evaluation. Study limitation includes lack of controls.

Measurement of Serum/Plasma Brain-Derived Neurotrophic Factor (BDNF) Levels as a Biomarker for Diagnosis of OSA

Khalaji et al (2022) stated that chronic intermittent hypoxia associated with OSA could affect neurons and glial cells, resulting in cell stress and damage, and changes in brain-derived neurotrophic factor (BDNF) levels. In a systematic review and meta-analysis, these investigators examined the relation between BDNF, OSA, and CPAP (the standard of care [SOC] in patients with OSA). A total of 5 databases were searched for studies that examined serum and/or plasma BDNF levels in patients with OSA and controls or publications examining the effect of CPAP treatment on BDNF levels. These investigators used SMDs with its 95 % CI comparison between patients with OSA and controls. A total of 10 studies were included in this meta-analysis examining the relation between BDNF levels, OSA, and CPAP treatment; 5 studies of BDNF levels in OSA compared to controls showed no significant difference (SMD = - 0.52, 95 % CI: - 1.93 to 0.89, p-value = 0.47). No statistically significant difference was found between CPAP

treatment in patients with OSA and BDNF levels (SMD = - 0.78, 95 % CI: - 1.77 to 0.21, p-value = 0.12). The authors concluded that BDNF peripheral levels were not significantly altered in OSA or by its related treatment, preventing its use as a biomarker.

Measurement of Serum/Plasma Insulin-Like Growth Factor 1 (IGF-1) Levels for Diagnosis of Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS)

He et al (2022) noted that OSAHS is a common disease that has serious cardiovascular and metabolic effects. Insulin-like growth factor 1 (IGF-1) levels are reportedly reduced in patients with OSAHS; however, this is still a matter of debate. In a meta-analysis, these investigators examined the association between serum/plasma IGF-1 levels and OSAHS. Wan Fang, Excerpta Medica dataBASE, Web of Science, China National Knowledge Infrastructure, VIP, PubMed, and other databases were searched for materials published in any language before April 2, 2022. Two researchers analyzed the studies for quality according to the Newcastle-Ottawa Scale. The acquired data were analyzed using Stata 11.0 and R 3.6.1 software. The effect size was estimated and calculated using SMDs and CIs. Moreover, a combined analysis was carried out using either a random- or fixed-effects model. A total of 34 studies met the inclusion criteria.

These findings showed that the plasma/serum IGF-1 concentrations in patients with OSAHS was significantly reduced compared with those in healthy subjects. Subgroup analyses were carried out according to OSAHS severity, ethnicity, age, BMI, specimen testing method, and study design. The outcomes suggested that nearly all subgroups of patients with OSAHS had reduced serum IGF-1 levels. Disease severity and differences in ethnicity were identified as possible influencing factors of serum IGF-1 levels in patients with OSAHS in the meta-regression analysis, and no other factors were found to alter plasma/serum IGF-1 concentrations. Moreover, plasma/serum IGF-1 concentrations were negatively correlated with AHI and oxygen desaturation index scores and positively associated with minimum oxygen saturation. The authors concluded that serum/plasma IGF-1 concentrations in patients with OSAHS were greatly reduced compared with those of patients in the control group; and were negatively correlated with AHI and oxygen desaturation index scores and positively correlated with minimum oxygen saturation. Moreover, these researchers stated that further well-designed studies are needed to examine the association between IGF-1 concentration and OSAHS risk.

The authors stated that this study had several drawbacks. First, this study may have included confounding variables, such as age, smoking history, lifestyle, alcohol consumption, sex, and diabetes. In particular, diabetes may be a major confounding factor for circulating IGF-1 levels. Moreover, OSA is more common in men, the elderly, and individuals with obesity compared with the general population. These investigators were unable to control for the afore-mentioned confounding factors because the included studies did not provide data on past medical history, specific lifestyle factors, or analysis by sex, and no studies were carried out only in older patients with OSAHS. To a greater or lesser extent, several potential confounding factors might have influenced the final findings. Second, the EEG fragmentation index and N3 sleep (SWS) were identified as important indicators in the evaluation of OSAHS; however, the included studies did not examine the direct relationship between serum/plasma IGF-1 levels, EEG fragmentation index and SWS. Third, these researchers were unable to conclude a causal association between serum/plasma IGF-1 concentrations and OSAHS in this investigation because of the lack of an appropriate longitudinal cohort study. Fourth, most of the studies included were small sample studies comprised of less than 100 cases, which was insufficient to confirm an association between IGF-1 and OSAHS.

Measurement of Serum/Plasma Monocyte Chemoattractant Protein-1 (MCP-1) Levels for Diagnosis of OSA

Imani et al (2022) stated that among the broad variety of chemokines, monocyte chemoattractant protein-1 (MCP-1) is considered to be one of the most important chemokines. Among others, MCP-1 activates monocytes and other immune cells highly involved in inflammation. In a systematic review and meta-analysis, these investigators examined the relationship between serum/plasma MCP-1 levels and the risk of OSA in adults as a disease related to inflammation. A total of 4 databases were systematically examined until July 12, 2022. These researchers employed the Review Manager 5.3 software to extract and calculate the SMD and its 95 % CI of plasma/serum levels of MCP-1 between adults with and without OSA. A total of 8 articles including 11 studies in adults were entered into the meta-analysis. The serum/plasma MCP-1 levels in adults with OSA were higher than that in the controls ($SMD = 0.81$; $p = 0.0007$) and as well as for adults with severe OSA compared to those with mild and moderate OSA ($SMD = 0.42$; $p < 0.0001$). The subgroup analysis showed that ethnicity was an effective factor in the pooled

analysis of blood MCP-1 levels in adults with OSA compared to the controls (Asians: ($p < 0.0001$), mixed ethnicity: ($p = 0.04$), and Caucasians: ($p = 0.89$)). The meta-regression showed increasing serum/plasma MCP-1 levels in adults with OSA versus the controls, publication year, age of controls, BMI of controls, and sample size reduced, and also BMI and the AHI of adults with OSA increased. The authors concluded that the findings of this meta-analysis showed that serum/plasma levels of MCP-1 in adults with OSA were significantly higher than those in controls, as well as in adults with severe OSA compared to mild/moderate OSA; thus, it appeared that MCP-1 could have a practical, clinical, and diagnostic importance in adults with OSA. In addition, age, ethnicity, BMI, and AHI should be considered in the diagnostic and therapeutic approach to adults with OSA.

The authors stated that this study had several drawbacks. First, there was a low number of cases in most of the studies. Second, there was a high heterogeneity in the initial pooled analysis. Third, the occurrence of several confounding factors. Fourth, some of the studies reported the MCP-1 level on the graphs and these researchers estimated their means (and SDs) with appropriate software. Fifth, there was a publication bias between or across the studies.

NightLase Laser Therapy for the Treatment of Snoring or Obstructive Sleep Apnea

The Fotona NightLase therapy is a non-invasive laser therapy used on the oral mucosa tissue for reducing the effects and amplitude of snoring.

Shiffman et al (2021) stated that OSA is a serious condition; however, its treatment is often not effective or is poorly accepted by patients. Newer modes of therapy that are more effective and also more accepted by patients need to be developed. The latest therapeutic approaches entail a minimally invasive LAUP procedure. This procedure involves thermal processing of the relaxed soft palate and surrounding tissues using neodymium-doped yttrium aluminum garnet (Nd:YAG) and erbium-doped yttrium aluminum garnet (Er:YAG) lasers, resulting in favorable collagen shrinkage and development of new collagen fibers. Procedure has previously been reported to safely and effectively reduce snoring, as well as increase the volume of the oropharyngeal airway, and is well-accepted by patients. These researchers examined the effectiveness of minimally invasive outpatient LAUP procedure (NightLase LAUP) to reduce AHI in patients with OSA. The

effectiveness of the minimally invasive LAUP procedure, combining Nd:YAG laser ($\lambda = 1,064$ nm) and Er:YAG laser ($\lambda = 2,940$ nm) applied to the soft palate for treatment of OSA on 27 patients with different severities of OSA was evaluated based on AHI measurements before and after only three 20-min sessions in an outpatient setting over a period of 45 to 60 days. A decrease in AHI for all the patients with different severities of OSA tested in this study was achieved, with 66.3 % average improvement (32 % to 100 %); and 50 % or more improvement was achieved in 78 % (21) of all patients. The authors concluded that based on these findings, the NightLase LAUP treatment of OSA represented a safe and effective therapeutic method. Moreover, these researchers stated that with further prospective, longer-term studies in a multi-disciplinary team to evaluate its effectiveness, this therapy could potentially be integrated into the current guidelines for treating OSA.

These investigators stated that one of the limitations of this trial was that AHI was used as a single endpoint demarcating success; however, a combination of patient-centered (scoring systems) and objective (PSG) outcomes would be preferable. Furthermore, these endpoints should ideally be interpreted together with at least some of the patient's other symptoms and anatomical characteristics (snoring score and reduction, Mallampati classification, Friedman tongue position, respiratory disturbance index, Muller's maneuver, etc.) and influence on QOL (satisfaction questionnaire, ESS, etc.). Even though AHI was only measured up to 1 month after the last treatment session, even better results could potentially be expected after 2 to 3 months when the process of neocollagenesis would be well established. According to the previous studies, the result of the NightLase treatment will typically last anywhere from 6 to 24 months and is easily touched up at follow-up appointments. Long-term effect of this treatment would need to be determined, but the analysis of charts was done retrospectively and the treatments and/or further objective evaluation of the outcome had been discontinued. It is also important to emphasize that if the obstruction responsible for OSA is not located in the oropharynx but, for example, in the nose or in the level of hyoid bone, the treatment will not be effective because these regions will not be irradiated with this protocol. Careful selection of patients with a multi-disciplinary approach is therefore critical.

In a RCT, Picavet et al (2022) examined the safety and effectiveness of a non-invasive 2,940 nm Er:YAG treatment with SMOOTH mode in reducing snoring in adult patients and compared its safety and effectiveness to sham treatment. A total of 40 primary snoring patients (18 years of age or older, AHI of less than 15 events/hour, BMI of 30 or less) were randomized to receive either 3 sessions NightLase or sham laser treatment. The main outcome measures were Snore Outcomes Survey (SOS), the Spouse/Bed Partner Survey (SBPS), a VAS scale (bed partner) and a VAS (pain). NightLase was well-tolerated, no local anesthesia was required (mean VAS pain score in NightLase group = 3.0 ± 1.7); no complications occurred. SOS, SBPS and VAS snoring scores improved in the NightLase group (33.7 ± 14.1 to 56.2 ± 16.1) (35.0 ± 17.1 to 61.5 ± 16.4) and (7.9 ± 2.0 to 4.7 ± 2.8) while no changing in the sham group (32.2 ± 14.5 versus 32.1 ± 13.0) (36.7 ± 12.1 versus 34.7 ± 12.7) (8.1 ± 1.7 versus 8.0 ± 1.6), respectively. The authors concluded that NightLase was a safe, minimal invasive treatment that significantly reduced snoring compared to sham treatment. Moreover, these researchers stated that further prospective, large-scale and long-term follow-up studies are needed to prove its (long-term) effectiveness. They stated that the findings of this trial are promising; moreover, not all subjects reported an adequate reduction of snoring. The small sample size ($n = 20$ in each group) and the short follow-up (up to 3 months after last treatment) limited the significance of the conclusions.

The ULTepap System

The ULTepap System is a single-patient, reusable expiratory positive airway pressure (EPAP) device for the treatment of mild-to-moderate OSA marketed as ULTepap, which received the FDA's 510(k) clearance on January 24, 2020. The device is comprised of a pair of bi-resistance cartridges that are designed and warrantied for a 3-year expected service life. The ULTepap System includes a headgear and appropriate size nasal pillow for the patient. These accessory items are similar in design and performance to currently available products.

An UpToDate review on "Obstructive sleep apnea: Overview of management in adults" (Kryger and Malhotra, 2023) does not mention ULTepap / expiratory positive airway pressure as a management / therapeutic option.

Glossary of Terms

Term	Definition
Apnea	Temporary cessation of breathing, especially during sleep
Apnea-hypopnea index (AHI)	Scale that measures sleep apnea severity, which includes the average number of episodes of apnea and hypopnea per hour
Automatic positive airway pressure (APAP)	Ventilation device that delivers positive air pressure which automatically self-adjusts based on a person's breathing and need to keep airway open
Bilevel positive airway pressure (BiPAP)	Ventilation device that delivers different positive air pressures upon inhaling (higher pressure) and exhaling (lower pressure) to keep airway open
Continuous positive airway pressure (CPAP)	Ventilation device that continuously delivers the same amount of positive air pressure during inspiration (inhaling) and expiration (exhalation) to keep airway open
Hypopnea	Partial reduction of airflow in the airway resulting in abnormally slow or shallow breathing
Obstructive sleep apnea (OSA)	Sleep-related breathing disorder that involves a decrease or complete halt in airflow despite an ongoing effort to breathe. It occurs when the muscles relax during sleep, causing soft tissue in the back of the throat to collapse and block the upper airway. This leads to hypopneas and apneas in breathing.
Positive airway pressure (PAP)	Uses a machine to pump air under pressure into the airway of the lungs
Polysomnography (PSG)	Sleep study; a comprehensive test used to diagnose sleep disorders
Positional therapy	Strategy for treating snoring and sleep apnea which involves wearing a device around the chest or waist to help prevent a person from laying in a supine position (on their back)

Respiratory disturbance index (RDI)	Combined number of apneas, hypopneas, and RERAs per hour of sleep
Respiratory effort related arousal (RERA)	Event that causes an arousal or a decrease in oxygen saturation, without qualifying as an apnea or hypopnea
Uvulopalatopharyngoplasty (UPPP)	Surgery to open the upper airways by taking out extra tissue in the throat
Upper airway stimulation (UAS) therapy	Involves implanting a small device that senses breathing patterns and delivers mild stimulation to a nerve in the throat with each breath to keep tissue in the throat and tongue from blocking the airway

Appendix

Link: [Tonsillar Hypertrophy Grading Scale](#)

(<https://fpnotebook.com/ent/Exam/TnslrHyprtrphyGrdngScl.htm>)

Indications for Obstructive Sleep Apnea Testing

Testing for OSA is considered medically necessary for individuals who present with clinical features suggestive of moderate to severe OSA as evidenced by:

I. Excessive daytime sleepiness (EDS) and ONE of the following are present:

- A. BMI greater than 30; *or*
- B. Excessive sleepiness while driving; *or*
- C. Loud/intense snoring; *or*

II. Epworth Sleepiness Scale (ESS) score of 10 or greater; *or*

III. Witnessed nocturnal apnea, choking and/or gasping.

Note: The International Classification of Sleep Disorders, third edition (ICSD-3) defines EDS as the inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentionally or at inappropriate times almost daily for at least three months (AASM, 2014).

Epworth Sleepiness Scale

Indicate the likelihood of falling asleep in the following commonly encountered situations. Assign the following scores to the patient's responses:

Table 1: Epworth Sleepiness Scale

Likelihood of dozing	Score
None	0
Low Chance	1
Moderate Chance	2
High Chance	3

1. Sitting and reading
2. Watching TV
3. Sitting, inactive, in a public place, i.e., theater
4. As a passenger in a car for an hour without a break
5. Lying down to rest in the afternoon when circumstances permit
6. Sitting and talking to someone
7. In a car, while stopped for a few minutes in traffic.

Sum the scores. A total greater than 10 is considered abnormal.

Monitoring Devices

Table 2: Monitoring Devices

Type	Devices	
I	Comprehensive standard overnight polysomnography in a sleep center or laboratory with a sleep technician in constant attendance.	Minimum of 7 parameters including EEG, EOG, chin EMG, ECG or heart rate, airflow, respiratory effort, oxygen saturation
II	Comprehensive, portable sleep study	Minimum of 7 parameters including EEG, EOG, chin EMG, ECG or heart rate, airflow, respiratory effort, oxygen saturation
III	Modified portable sleep apnea testing	Minimum of 4 parameters, including ventilation (at least 2 channels of respiratory movement, or respiratory movement and airflow), heart rate or ECG, oxygen saturation)
IV(A)	Three or more bioparameters	Airflow and at least 2 other parameters (e.g., EOG, peripheral arterial tonometry (PAT), snoring, actigraphy, pulse oximetry)
IV(B)	Continuous single- or dual-bioparameter recording	Minimum of 1 parameter (e.g., overnight oximetry) and does not meet criteria for Types I to III or Type IV(A) device.

Usual Medically Necessary Quantities of Positive Airway Pressure Supplies

Table 3: Usual Medically Necessary Quantities of Positive Airway Pressure Supplies

Supply Description	Quantity
Tubing with integrated heating element for use with positive airway pressure device	1 per 3 months
Combination oral/nasal mask, used with continuous positive airway pressure, each	1 per 3 months

Oral cushion for combination oral/nasal mask, replacement only	2 per 1 month
Nasal pillows for combination oral/nasal mask	2 per 1 month
Full face mask used with positive airway pressure device	1 per 3 months
Full face mask interface, replacement for full face mask	1 per 1 month
Cushion for use on nasal mask interface	2 per 1 month
Pillow for use on nasal cannula type interface	2 per 1 month
Nasal interface (mask or cannula type, used with positive aiway pressure	1 per 3 months
Headgear used with positive airway pressure device	1 per 6 months
Chinstrap used with positive airway pressure device	1 per 6 months
Tubing used with positive airway pressure device	1 per 3 months
Filter, disposable, used with positive airway pressure devcie	2 per 1 month
Filter, nondisposable, used with positive airway pressure device	1 per 6 months
Water chamber for humidifier, used with positie airway pressure	1 per 6 months

References

The above policy is based on the following references:

1. Adil EA. Uvulopalatopharyngoplasty. Medscape. New York, NY: Medscape; October 6, 2017. Available at: <https://emedicine.medscape.com/article/1942134-overview>. Accessed October 13, 2017.
2. Afonso Delgado L, Micoulaud Franchi JA, Monteyrol PJ, Philip P. Implantable nerve stimulation for obstructive sleep apnea hypopnea syndrome. Presse Med. 2016;45(2):183-192.

3. Agency for Healthcare Policy and Research (AHCPR). Systematic review of the literature regarding the diagnosis of sleep apnea. Evidence Report/Technology Assessment No. 1. AHCPR Publication No. 99-E002. Bethesda, MD: AHCPR; December 1998.
4. Agency for Healthcare Research and Quality (AHRQ), Technology Assessment Program. Effectiveness of portable monitoring devices for diagnosing obstructive sleep apnea: Update of a systematic review. Technology Assessment. Final Report. Prepared by RTI International for AHRQ. Rockville, MD: AHRQ; September 1, 2004.
5. Alberta Heritage Foundation for Medical Research (AHFMR). Radiofrequency ablation of excess tongue tissue. Emerging Technology Report. Edmonton, AB: AHFMR; 1999.
6. Alberta Heritage Foundation for Medical Research (AHFMR). RF tonsillar ablation. Emerging Technology Report. Edmonton, AB: AHFMR; 2000.
7. Alberta Heritage Foundation for Medical Research (AHFMR). Somnoplasty system. Emerging Technology Report. Edmonton, AB: AHFMR; 2000.
8. Aloia MS, Stanchina M, Arnedt JT, et al. Treatment adherence and outcomes in flexible vs. standard continuous positive airway pressure therapy. *Chest*. 2005;127(6):2085-2093.
9. American Academy of Otolaryngology (AAO). Position statement: Hypoglossal nerve stimulation for treatment of obstructive sleep apnea (OSA). Alexandria, VA: AAO; March 20, 2016. Available at: <http://www.entnet.org/content/position-statement-hypoglossal-nerve-stimulation-treatment-obstructive-sleep-apnea-osa>. Accessed April 11, 2018.
10. American Academy of Pediatrics. Clinical practice guideline: Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2002;109(4):704-712.
11. American Academy of Sleep Medicine (AASM). International Classification of Sleep Disorders, 3rd ed. Darien, IL: AASM; 2014.
12. American Academy of Sleep Medicine (AASM). Obstructive sleep apnea. Fact Sheet. Darien, IL: American Academy of Sleep Medicine; 2008. Available at <http://www.aasmnet.org/Resources/FactSheets/SleepApnea.pdf>. Accessed October 29, 2013.
13. American Academy of Sleep Medicine, Standards of Practice Committee. Practice parameters for the use of auto-titrating continuous positive airway pressure devices for titrating pressures and treating adult patients with obstructive sleep apnea. *Sleep*. 2002;25(2):143-147.

14. American Sleep Disorders Association, Standards of Practice Committee, Polysomnography Task Force. Practice parameters for the indications for polysomnography and related procedures. *Sleep*. 1997;20(6):406-422.
15. American Sleep Disorders Association, Standards of Practice Committee. Practice parameter for the use of portable recording of the assessment of obstructive sleep apnea. *Sleep*. 1994;17(4):372-377.
16. American Sleep Disorders Association, Standards of Practice Committee. Practice parameters for the use of laser-assisted uvulopalatoplasty: An American Sleep Disorders Association Report. *Sleep*. 1994;17(8):744-748.
17. American Sleep Disorders Association. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances. *Sleep*. 1995;18(6):511-513.
18. American Sleep Disorders Association. Practice parameters for the treatment of obstructive sleep apnea in adults: The efficacy of surgical modifications of the upper airway. Report of the American Sleep Disorders Association. *Sleep*. 1996;19:152-155.
19. Atkins JH, Mandel JE. Drug-induced sleep endoscopy: From obscure technique to diagnostic tool for assessment of obstructive sleep apnea for surgical interventions. *Current Opinion in Anaesthesiology*. 2018; 31(1):120-126.
20. Aurora RN, Casey KR, Kristo D, et al. Practice parameters for the surgical modifications of the upper airway for obstructive sleep apnea in adults. *Sleep*. 2010;33(10):1409-1413.
21. Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S). Rapid Review - Upper airway surgery for the treatment of adult obstructive sleep apnoea. ASERNIP-S Report No. 67. Stepney, SA: Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S); 2008.
22. Ayas NT, Patel SR, Malhotra A, et al. Auto-titrating versus standard continuous positive airway pressure for the treatment of obstructive sleep apnea: Results of a meta-analysis. *Sleep*. 2004;27(2):249-253.
23. Back L, Palomaki M, Piilonen A, Ylikoski J. Sleep-disordered breathing: Radiofrequency thermal ablation is a promising new treatment possibility. *Laryngoscope*. 2001;111(3):464-471.
24. Baker Tilly, LLP. Inspire hypoglossal nerve stimulator dossier. New York, NY. Received November 8, 2017.

25. Banno K, Kryger MH. Sleep apnea: Clinical investigations in humans. *Sleep Med.* 2007;8(4):400-426.
26. Banno K, Okamura K, Kryger MH. Adaptive servo-ventilation in patients with idiopathic Cheyne-Stokes breathing. *J Clin Sleep Med.* 2006;2(2):181-186.
27. Baptista PM, Martínez Ruiz de Apodaca P, Carrasco M, et al. Daytime neuromuscular electrical therapy of tongue muscles in improving snoring in individuals with primary snoring and mild obstructive sleep apnea. *J Clin Med.* 2021;10(9):1883.
28. Barnes H, Edwards BA, Joosten SA, et al. Positional modification techniques for supine obstructive sleep apnea: A systematic review and meta-analysis. *Sleep Med Rev.* 2017;36:107-115.
29. Barone DA. Alternative devices for obstructive sleep apnea. *Neurol Clin Pract.* 2013;3(1):67-70.
30. Becker HF, Jerrentrup A, Ploch T, et al. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation.* 2003;107(1):68-73.
31. Benoist LBL, Vonk PE, de Vries N, et al. New-generation positional therapy in patients with positional central sleep apnea. *Eur Arch Otorhinolaryngol.* 2019;276(9):2611-2619.
32. Berry RB, Kryger MH, Massie CA. A novel nasal expiratory positive airway pressure (EPAP) device for the treatment of obstructive sleep apnea: A randomized controlled trial. *Sleep.* 2011;34(4):479-485.
33. Berry RB, Parish JM, Hartse KM. The use of auto-titrating continuous positive airway pressure for treatment of adult obstructive sleep apnea. *Sleep.* 2002;25(2):148-173.
34. Bloch KE, Iseli A, Zhang JN, et al. A randomized, controlled crossover trial of two oral appliances for sleep apnea treatment. *Am J Respir Crit Care Med.* 2000;162(1):246-251.
35. Blumen MB, Dahan S, Fleury B, et al. Radiofrequency ablation for the treatment of mild to moderate obstructive sleep apnea. *Laryngoscope.* 2002;112(11):2086-2092.
36. Blumen MB, Dahan S, Wagner I, et al. Radiofrequency versus LAUP for the treatment of snoring. *Otolaryngol Head Neck Surg.* 2002;126(1):67-73.
37. Bouudewyns A, Van De Heyning P. Temperature-controlled radiofrequency tissue volume reduction of the soft palate (somnoplasty) in the treatment of habitual snoring: Results of a European multicenter trial. *Acta Otolaryngol.* 2000;120(8):981-985.

38. Brietzke SE, Gallagher D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: A meta-analysis. *Otolaryngol Head Neck Surg.* 2006;134(6):979-984.
39. Brietzke SE, Mair EA. Injection snoreplasty: How to treat snoring without all the pain and expense. *Otolaryngol Head Neck Surg.* 2001;125(5):579-580.
40. Brown DJ, Kerr P, Kryger M. Radiofrequency tissue reduction of the palate in patients with moderate sleep-disordered breathing. *J Otolaryngol.* 2001;30(4):193-198.
41. Brown LK. Back to basics: If it's dry, wet it. The case for humidification of nasal continuous positive airway pressure air. *Chest.* 2000;117(3):617-169.
42. Byun YJ, Yan F, Nguyen SA, Lentsch EJ. Transcutaneous electrical stimulation therapy in obstructive sleep apnea: A systematic review and meta-analysis. *Otolaryngol Head Neck Surg.* 2020;163(4):645-653.
43. Busaba N, Doron S. Tonsillectomy in adults: Indications. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed Dec 2015.
44. Cahali MB, Formigoni GG, Gebrim EM, Miziara ID. Lateral pharyngoplasty versus uvulopalatopharyngoplasty: A clinical, polysomnographic and computed tomography measurement comparison. *Sleep.* 2004;27(5):942-950.
45. Camacho M, Chang ET, Song SA, et al. Rapid maxillary expansion for pediatric obstructive sleep apnea: A systematic review and meta-analysis. *Laryngoscope.* 2017;127(7):1712-1719.
46. Canadian Agency for Drugs and Technologies in Health (CADTH). Obstructive sleep apnea: A palatable treatment option? Issues in Emerging health Technologies, Issue 97. Ottawa, ON: CADTH; January 2007.
47. Canadian Agency for Drugs and Technologies in Health (CADTH). Portable monitoring devices for diagnosis of obstructive sleep apnea at home: Review of accuracy, cost-effectiveness, guidelines, and coverage in Canada. Ottawa, ON: CADTH; December 2009.
48. Cao Y, Song Y, Ning P, et al. Association between tumor necrosis factor alpha and obstructive sleep apnea in adults: A meta-analysis update. *BMC Pulm Med.* 2020;20(1):215.
49. Caples SM, Rowley JA, Prinsell JR, et al. Surgical modifications of the upper airway for obstructive sleep apnea in adults: A systematic review and meta-analysis. *Sleep.*

2010;33(10):1396-1407.

50. Catalfumo FJ, Golz A, Westerman ST, et al. The epiglottis and obstructive sleep apnoea syndrome. *J Laryngol Otol*. 1998;112(10):940-943.
51. Center for Medicare and Medicaid Services (CMS). Decision memo for continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea (OSA) (CAG-00093R). Medicare Coverage Database. Baltimore, MD: CMS; April 4, 2005.
52. Centers for Medicare & Medicaid Services (CMS). Decision memo for sleep testing for obstructive sleep apnea (OSA) (CAG-00405N). Medicare Coverge Database. Baltimore, MD: CMS; March 3, 2009.
53. Cortal VF, Zaghi S, Riaz M, et al. Hypoglossal nerve stimulation in the treatment of obstructive sleep apnea: A systematic review and meta-analysis. *Laryngoscope*. 2015;125(5):1254-1264.
54. Chai CL, Pathinathan A, Smith B. Continuous positive airway pressure delivery interfaces for obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2006;(4):CD005308.
55. Chang HP, Chen YF, Du JK. Obstructive sleep apnea treatment in adults. *Kaohsiung J Med Sci*. 2020;36(1):7-12.
56. Chesson AL Jr, Ferber RA, Fry JM, et al. The indications for polysomnography and related procedures. *Sleep*. 1997;20(6):424-487.
57. Chesson AL, Jr, Berry RB, Pack A. Practice parameters for the use of portable monitoring devices in the investigation of suspected obstructive sleep apnea in adults. *American Academy of Sleep Medicine. Sleep*. 2003;26(7):907-913.
58. Chi JC, Chiang RP, Chou TY, et al. The role of lateral pharyngoplasty in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 2015;272(2):489-496.
59. Chihorek AM, Abou-Khalil B, Malow BA. Obstructive sleep apnea is associated with seizure occurrence in older adults with epilepsy. *Neurology*. 2007;69(19):1823-1827.
60. Cistulli PA. Oral appliances in the treatment of obstructive sleep apnea in adults. *UpToDate [online serial]*. Waltham, MA: UpToDate; reviewed September 2017.
61. Clements AC, Dai X, Walsh JM, et al. Outcomes of adenotonsillectomy for obstructive sleep apnea in Prader-Willi syndrome: Systematic review and meta-analysis. *Laryngoscope*. 2021;131(4):898-906
62. Coleman J, Bick PA. Suspension sutures for the treatment of obstructive sleep apnea and snoring. *Otolaryngol Clin North Am*. 1999;32(2):277-285.

63. Coleman J. Sleep studies. Current techniques and future trends. *Otolaryngol Clin North Am.* 1999;32(2):195-210.
64. Collop NA, Anderson WM, Boehlecke B, et al.; Portable Monitoring Task Force of the American Academy of Sleep Medicine. 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(7):737-747.
65. Colrain IM, Black J, Siegel LC, et al. A multicenter evaluation of oral pressure therapy for the treatment of obstructive sleep apnea. *Sleep Med.* 2013;14(9):830-837.
66. Colrain IM, Brooks S, Black J. A pilot evaluation of a nasal expiratory resistance device for the treatment of obstructive sleep apnea. *J Clin Sleep Med.* 2008;4(5):426-433.
67. Dafna E, Tarasiuk A, Zigel Y. Sleep-quality assessment from full night audio recordings of sleep apnea patients. *Conf Proc IEEE Eng Med Biol Soc.* 2012;2012:3660-3663.
68. D'Andrea LA. Diagnostic studies in the assessment of pediatric sleep-disordered breathing: Techniques and indications. *Pediatr Clin North Am.* 2004;51(1):169-186.
69. Danish Centre for Evaluation and Health Technology Assessment (DACEHTA). Diagnosis and treatment of obstructive sleep apnoea - a health technology assessment. Danish Health Technology Assessment -- grant funded projects. Copenhagen, Denmark; DACEHTA; 2006;6(5).
70. Dawodu ST. Swallowing disorders. eMedicine Physical Medicine & Rehabilitation Topic 152. Omaha, NE: eMedicine.com; updated January 26, 2007.
71. de Paula Soares CF, Cavichio L, Cahali MB. Lateral pharyngoplasty reduces nocturnal blood pressure in patients with obstructive sleep apnea. *Laryngoscope.* 2014;124(1):311-316.
72. DeRowe A, Gunther E, Fibbi A, et al. Tongue-base suspension with a soft tissue-to-bone anchor for obstructive sleep apnea: Preliminary clinical results of a new minimally invasive technique. *Otolaryngol Head Neck Surg.* 2000;122(1):100-103.
73. Dizdar D, Civelek S, Calis ZA, et al. Comparative analysis of lateral pharyngoplasty and uvulopalatopharyngoplasty techniques with polisomnography and Epworth sleepiness scales. *J Craniofac Surg.* 2015;26(7):e647-e651.
74. Domagała-Kulawik J, Kwiecien I, Bielicki P, Skirecki T. Fas-positive lymphocytes are associated with systemic inflammation in obstructive sleep apnea syndrome. *Sleep*

Breath. 2019;23(2):673-678.

75. Eisele DW, Schwartz AR, Smith PL. Tongue neuromuscular and direct hypoglossal nerve stimulation for obstructive sleep apnea. *Otolaryngol Clin North Am.* 2003;36(3):501-510.
76. Eisele DW, Smith PL, Alam DS, et al. Direct hypoglossal nerve stimulation in obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg.* 1997;123(1):57-61.
77. El Shayeb M, Topfer LA, Stafinski T, et al. Diagnostic accuracy of level 3 portable sleep tests versus level 1 polysomnography for sleep-disordered breathing: A systematic review and meta-analysis. *CMAJ.* 2014;186(1):E25-E51.
78. Epstein LJ, Dorlac GR. Cost-effectiveness analysis of nocturnal oximetry as a method of screening for sleep apnea-hypopnea syndrome. *Chest.* 1998;113(1):97-103.
79. Epstein LJ, Kristo D, Strollo PJ Jr, et al; Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med.* 2009;5(3):263-276.
80. Farid-Moayer M, Siegel LC, Black J. A feasibility evaluation of oral pressure therapy for the treatment of obstructive sleep apnea. *Ther Adv Respir Dis.* 2013;7(1):3-12.
81. Fadaei R, Safari-Faramani R, Hosseini H, et al. Increased the circulating levels of malondialdehyde in patients with obstructive sleep apnea: A systematic review and meta-analysis. *Sleep Breath.* 2021;25(4):1753-1760.
82. Farid-Moayer M, Siegel LC, Black J. Oral pressure therapy for treatment of obstructive sleep apnea: Clinical feasibility. *Nature and Science of Sleep.* 2013;5:53-59.
83. Ferguson K. Oral appliance therapy for obstructive sleep apnea: Finally evidence you can sink your teeth into. *Am J Respir Crit Care Med.* 2001;163(6):1294-1295.
84. Ferguson KA, Cartwright R, Rogers R, et al. Oral appliances for snoring and obstructive sleep apnea: A review. *Sleep.* 2006;29(2):244-262.
85. Fernandez-Julian E, Munoz N, Achiques MT, et al. Randomized study comparing two tongue base surgeries for moderate to severe obstructive sleep apnea syndrome. *Otolaryngol Head Neck Surg.* 2009;140(6):917-923.
86. Fibbi A, Presta A, Fasciolo G. The REPOSE system. *Acta Otorhinolaryngol Ital.* 1999;19(1):21-25.
87. Findley L, Smith C, Hooper J, et al. Treatment with nasal CPAP decreases automobile accidents in patients with sleep apnea. *Am J Respir Crit Care Med.* 2000;161(3 Pt 1):857-

88. Fletcher EC, Stich J, Yang KL. Unattended home diagnosis and treatment of obstructive sleep apnea without polysomnography. *Arch Fam Med*. 2000;9(2):168-174.
89. Folk D, D'Agostino M. Transoral robotic surgery vs. endoscopic partial midline glossectomy for obstructive sleep apnea. *World J Otorhinolaryngol Head Neck Surg*. 2017;3(2):101-105.
90. Friedman M, Vidyasagar R, Bliznikas D, Joseph NJ. Patient selection and efficacy of Pillar implant technique for treatment of snoring and obstructive sleep apnea/hypopnea syndrome. *Otolaryngol Head Neck Surg*. 2006;134(2):187-196.
91. Fujita S, Conway WA, Zorick FJ. Evaluation of the effectiveness of uvulopalatopharyngoplasty. *Laryngoscope*. 1985;95:70-75.
92. Garcia GJM, Woodson BT. The collapsing anatomical structure is not always the primary site of flow limitation in obstructive sleep apnea. *J Clin Sleep Med*. 2020;16(3):345-346.
93. Garrigue S, Bordier P, Jais P, et al. Benefit of atrial pacing in sleep apnea syndrome. *N Engl J Med*. 2002;346(6):404-412.
94. Ghegan MD, Angelos PC, Stonebraker AC, et al. Laboratory versus portable sleep studies: A meta-analysis. *Laryngoscope*. 2006;116(6):859-864.
95. Giles TL, Lasserson TJ, Smith BH, et al. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev*. 2006;3:CD001106.
96. Gillespie MB, Soose RJ, Woodson BT; STAR Trial Investigators. Upper airway stimulation for obstructive sleep apnea: Patient-reported outcomes after 48 months of follow-up. *Otolaryngol Head Neck Surg*. 2017;156(4):765-771.
97. Gillespie MB, Wylie PE, Lee-Chiong T, Rapoport DM. Effect of palatal implants on continuous positive airway pressure and compliance. *Otolaryngol Head Neck Surg*. 2011;144(2):230-236.
98. Golz A, Goldenberg D, Westerman ST, et al. Laser partial epiglottidectomy as a treatment for obstructive sleep apnea and laryngomalacia. *Ann Otol Rhinol Laryngol*. 2000;109(12 Pt 1):1140-1145.
99. Gotspoulos H, Chen C, Qian J, Cistulli PA. Oral appliance therapy improves symptoms in obstructive sleep apnea: A randomized, controlled trial. *Am J Respir Crit Care Med*. 2002;166(5):743-748.

100. Gottlieb DJ. Cardiac pacing - a novel therapy for sleep apnea? *N Engl J Med.* 2002;346(6):444-445.
101. Guilleminault C, Chervin R, Palombini L, et al. Radiofrequency (pacing and thermic effects) in the treatment of sleep-disordered breathing. *Sleep.* 2000;23 Suppl 4:S182-S186.
102. Guilleminault C, Khramtsov A. Upper airway resistance syndrome in children: A clinical review. *Semin Pediatr Neurol.* 2001;8(4):207-215.
103. Guilleminault C, Stoohs R, Clerk A, et al. A cause of daytime sleepiness. The upper airway resistance syndrome. *Chest.* 1993;104(3):781-787.
104. Hailey D, Jacobs P, Mayers I, Mensinkai S. Auto-titrating nasal continuous positive airway pressure systems in the management of obstructive sleep apnea. Technology Report 39. Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); September 2003.
105. Hailey D, Tran K, Dales R, et al. A review of guidelines for referral of patients to sleep laboratories. Technology Report. Issue 55. Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2005.
106. Hamans E, Boudewyns A, Stuck BA, et al. Adjustable tongue advancement for obstructive sleep apnea: A pilot study. *Ann Otol Rhinol Laryngol.* 2008;117(11):815-823.
107. Haniffa M, Lasserson TJ, Smith I. Interventions to improve compliance with continuous positive airway pressure for obstructive sleep apnoea. *Cochrane Database Syst Rev.* 2004;(4):CD003531.
108. Hastings PC, Vazir A, Meadows GE, et al. Adaptive servo-ventilation in heart failure patients with sleep apnea: A real world study. *Int J Cardiol.* 2010;139(1):17-24.
109. Hawke M, Kwok P. Acute inflammatory edema of the uvula (uvulitis) as a cause of respiratory distress: A case report. *J Otolaryngol.* 1987;16(3):188-190.
110. Hayes MJ, McGregor FB, Roberts DN, et al. Continuous nasal positive airway pressure (nasal CPAP) with a mouth leak: Effect on nasal mucosal blood flux and nasal geometry. *Thorax.* 1995;50(11):1179-1182.
111. He J, Li X, Yu M, et al. The correlation of serum/plasma IGF-1 concentrations with obstructive sleep apnea hypopnea syndrome: A meta-analysis and meta-regression. *Front Endocrinol (Lausanne).* 2022;13:922229.

112. Heinzer R, Gaudreau H, Décarie A, et al. Slow-wave activity in sleep apnea patients before and after continuous positive airway pressure treatment. Contribution to daytime sleepiness. *Chest*. 2001;119(6):1807-1813.
113. Heiser C, Maurer JT, Hofauer B, et al. Outcomes of upper airway stimulation for obstructive sleep apnea in a multicenter German postmarket study. *Otolaryngol Head Neck Surg*. 2017;156(2):378-384.
114. Henke K, Frantz DE, Kuna ST. An oral elastic mandibular advancement device for obstructive sleep apnea. *Am J Respir Crit Care Med*. 2000;161:420-425.
115. Hensley N, Ray C. Sleep apnoea. In: BMJ Clinical Evidence. London, UK: BMJ Publishing Group; May 2008.
116. Hillberg RE, Johnson DC. Current concepts: Noninvasive ventilation. *N Engl J Med*. 1997;337(24):1746-1752.
117. Hofauer B, Philip P, Wirth M, et al. Effects of upper-airway stimulation on sleep architecture in patients with obstructive sleep apnea. *Sleep Breath*. 2017;21(4):901-908.
118. Hoffstein V, Viner S, Mateika S, Conway J. Treatment of obstructive sleep apnea with nasal continuous airway pressure: Patient compliance, perception of benefits and side effects. *Am Rev Respir Dis*. 1992;145(4 Pt 1):841-845.
119. Hsu B, Emperumal CP, Grbach VX, et al. Effects of respiratory muscle therapy on obstructive sleep apnea: A systematic review and meta-analysis. *J Clin Sleep Med*. 2020;16(5):785-801.
120. Huang T, Goodman M, Li X, et al. C-reactive protein and risk of OSA in four US cohorts. *Chest*. 2021;159(6):2439-2448.
121. Huntley C, Kaffenberger T, Doghramji K, et al. Upper airway stimulation for treatment of obstructive sleep apnea: An evaluation and comparison of outcomes at two academic centers. *Journal of Clinical Sleep Medicine: JCSM: Official Publication of the American Academy of Sleep Medicine*. 2017;13(9):1075-1079.
122. Hur J-S, Kim H-H, Choi J-Y, et al. Investigation of the effects of miniscrew-assisted rapid palatal expansion on airflow in the upper airway of an adult patient with obstructive sleep apnea syndrome using computational fluid-structure interaction analysis. *Korean J Orthod*. 2017;47(6):353-364.
123. Imani MM, Sadeghi M, Farokhzadeh F, et al. Evaluation of blood levels of C-reactive protein marker in obstructive sleep apnea: A systematic review, meta-analysis and

meta-regression. *Life (Basel)*. 2021;11(4):362.

124. Imani MM, Sadeghi M, Khazaie H, et al. Evaluation of serum and plasma interleukin-6 levels in obstructive sleep apnea syndrome: A meta-analysis and meta-regression. *Front Immunol*. 2020a;11:1343.
125. Imani MM, Sadeghi M, Khazaie H, et al. Serum and plasma tumor necrosis factor alpha levels in individuals with obstructive sleep apnea syndrome: A meta-analysis and meta-regression. *Life (Basel)*. 2020b;10(6):87.
126. Imani MM, Sadeghi M, Mohammadi M, et al. Association of blood MCP-1 levels with risk of obstructive sleep apnea: A systematic review and meta-analysis. *Medicina (Kaunas)*. 2022;58(9):1266.
127. Inspire Medical Systems, Inc. Inspire Medical Systems announces FDA approval of Inspire 3028 neurostimulator for the treatment of obstructive sleep apnea. Press Release. Minneapolis, MN: Inspire; June 5, 2017.
128. Inspire Medical Systems, Inc. Inspire system implant manual. Maple Grove, MN: Inspire; 2014. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130008D.pdf. Accessed April 12, 2018.
129. Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of obstructive sleep apnea. Health Care Guideline. 4th ed. Bloomington, MN: ISCI; March 2006.
130. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. *Circulation*. 2000;101(4):392-397.
131. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med*. 2017;13(3):479-504.
132. Karakoc O, Akcam MT, Genc H, et al. Do pharyngeal surgeries for snoring and obstructive sleep apnea have an impact on nasalalance scores? *J Craniofac Surg*. 2015;26(7):2213-2216.
133. Kasai T, Narui K, Dohi T, et al. First experience of using new adaptive servo-ventilation device for Cheyne-Stokes respiration with central sleep apnea among Japanese patients with congestive heart failure: Report of 4 clinical cases. *Circ J*. 2006;70(9):1148-1154.
134. Kastoer C, Dieltjens M, Oorts E, et al. The use of remotely controlled mandibular positioner as a predictive screening tool for mandibular advancement device therapy in

- patients with obstructive sleep apnea through single-night progressive titration of the mandible: A systematic review. *J Clin Sleep Med.* 2016;12(10):1411-1421.
135. Kent DT, Carden KA, Wang L, et al. Evaluation of hypoglossal nerve stimulation treatment in obstructive sleep apnea. *JAMA Otolaryngol Head Neck Surg.* 2019;145(11):1044-1052.
136. Kent DT, Zealear D, Schwartz AR, et al. Ansa cervicalis stimulation: A new direction in neurostimulation for OSA. *Chest.* 2021;159(3):1212-1221.
137. Kezirian EJ, Boudewyns A, Eisele DW, et al. Electrical stimulation of the hypoglossal nerve in the treatment of obstructive sleep apnea. *Sleep Med Rev.* 2010;14(5):299-305.
138. Khalaji A, Behnoush AH, Shobeiri P, et al. Association between brain-derived neurotrophic factor levels and obstructive sleep apnea: A systematic review and meta-analysis. *Sleep Breath.* 2022 Sep 17 [Online ahead of print].
139. Kingshott RN, Vennelle M, Hoy CJ, et al. Predictors of improvements in daytime function outcomes with CPAP therapy. *Am J Respir Crit Care Med.* 2000;161(3 Pt 1):866-871.
140. Kirk V, Baughn J, D'Andrea L, et al. American Academy of Sleep Medicine position paper for the use of a home sleep apnea test for the diagnosis of OSA in children. *J Clin Sleep Med.* 2017;13(10):1199-1203.
141. Kitamura K, Shimizu M, Yatomi M, et al. The efficacy of genioglossus advancement and uvulopalatopharyngoplasty for obstructive sleep apnea syndrome. *Nihon Jibiinkoka Gakkai Kaiho.* 2014;117(5):645-652.
142. Kohler M, Bloch KE, Stradling JR. The role of the nose in the pathogenesis of obstructive sleep apnoea and snoring. *Eur Respir J.* 2007;30(6):1208-1215.
143. Koutsourelakis I, Georgoulopoulos G, Perraki E, et al. Randomised trial of nasal surgery for fixed nasal obstruction in obstructive sleep apnoea. *Eur Respir J.* 2008;31(1):110-117.
144. Krahn AD, Yee R, Erickson MK, et al. Physiologic pacing in patients with obstructive sleep apnea: A prospective, randomized crossover trial. *J Am Coll Cardiol.* 2006;47(2):379-383.
145. Krieger J. Long-term compliance with nasal continuous positive airway pressure (CPAP) in obstructive sleep apnea patients and nonapneic snorers. *Sleep.* 1992;15(6):S42-S46.
146. Kryger MH. Management of obstructive sleep apnea in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed September 2013.
147. Kryger MH, Berry RB, Massie CA. Long-term use of a nasal expiratory positive airway pressure (EPAP) device as a treatment for obstructive sleep apnea (OSA). *J Clin Sleep*

Med. 2011;7(5):449-453.

148. Kryger MH, Malhotra A. Management of obstructive sleep apnea in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed November 2014.
149. Kryger MH, Malhotra A. Management of obstructive sleep apnea in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed August 2016.
150. Kryger MH, Malhotra A. Management of obstructive sleep apnea in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed September 2017.
151. Kryger MH, Mohotra A. Management of obstructive sleep apnea in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed November 2015.
152. Kryger MH, Malhotra A. Obstructive sleep apnea: Overview of management in adults. UpToDate Inc., Waltham, MA. Last reviewed February 2023.
153. Kuhnel TS, Schurr C, Wagner B, Geisler P. Morphological changes of the posterior airway space after tongue base suspension. *Laryngoscope*. 2005;115(3):475-480.
154. Kushida CA, Littner MR, Hirshkowitz M, et al; American Academy of Sleep Medicine. 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(3):375-380.
155. Kushida CA, Morgenthaler TI, Littner MR, et al.; American Academy of Sleep Medicine. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: An update for 2005. *Sleep*. 2006;29(2):240-243.
156. Lacassagne L, Didier A, Murris-Espin M, et al. Role of nocturnal oximetry in screening for sleep apnea syndrome in pulmonary medicine. Study of 329 patients. *Rev Mal Respir*. 1997;14(3):201-207.
157. Lan MC, Liu SY, Lan MY, et al. Lateral pharyngeal wall collapse associated with hypoxemia in obstructive sleep apnea. *Laryngoscope*. 2015;125(10):2408-2412.
158. Lee JB, Park YH, Hong JH, et al. Determining optimal sleep position in patients with positional sleep-disordered breathing using response surface analysis. *J Sleep Res*. 2009;18(1):26-35.
159. Lee JM, Weinstein GS, O'Malley BW Jr, Thaler ER. Transoral robot-assisted lingual tonsillectomy and uvulopalatopharyngoplasty for obstructive sleep apnea. *Ann Otol Rhinol Laryngol*. 2012;121(10):635-639.

160. Levy P, Pepin JL, Deschaux-Blanc C, et al. Accuracy of oximetry for detection of respiratory disturbances in sleep apnea syndrome. *Chest*. 1996;109(2):395-399.
161. Li K, Quo S, Guilleminault C. Endoscopically-assisted surgical expansion (EASE) for the treatment of obstructive sleep apnea. *Sleep Med*. 2019;60:53-59.
162. Li X, He J. The association between serum/plasma leptin levels and obstructive sleep apnea syndrome: A meta-analysis and meta-regression. *Front Endocrinol (Lausanne)*. 2021;12:696418.
163. Li X, Hu R, Ren X, He J. Interleukin-8 concentrations in obstructive sleep apnea syndrome: A systematic review and meta-analysis. *Bioengineered*. 2021;12(2):10666-10681.
164. Lim J, Lasserson TJ, Fleetham J, Wright J. Oral appliances for obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2006;(1):CD004435.
165. Lin HC, Friedman M, Chang HW, Gurpinar B. The efficacy of multilevel surgery of the upper airway in adults with obstructive sleep apnea/hypopnea syndrome. *Laryngoscope*. 2008;118(5):902-908.
166. Littner M, Hirshkowitz M, Davila D, et al.; Standard of Practice Committee of the American Academy of Sleep Medicine (AASM). 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. *Sleep*. 2002;25(2):143-147.
167. Littner M, Hirshkowitz M, Kramer M, et al. Practice parameters for using polysomnography to evaluate insomnia: An update. *American Academy of Sleep Medicine*. Published September 2003. Available at: <http://www.aasmnet.org/practiceparameters.asp>. Accessed January 6, 2004.
168. Littner M, Kushida CA, Anderson WM, et al. Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: An update for 2002. *Sleep*. 2003;26(3):337-341.
169. Littner M, Kushida CA, Hartse K, et al. Practice parameters for the use of laser-assisted uvulopalatoplasty: An update for 2000. *Sleep*. 2001;24(5):603-619.
170. 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(1):113-121.
171. Loube DI, Gay PC, Strohl KP, et al. Indications for positive airway pressure treatment of adult obstructive sleep apnea patients: A consensus statement. *Chest*. 1999;115(3):863-

172. Luthje L, Unterberg-Buchwald C, Dajani D, et al. Atrial overdrive pacing in patients with sleep apnea with implanted pacemaker. *Am J Respir Crit Care Med.* 2005;172(1):118-122.
173. Machado-Junior AJ, Zancanella E, Crespo AN. Rapid maxillary expansion and obstructive sleep apnea: A review and meta-analysis. *Med Oral Patol Oral Cir Bucal.* 2016;21(4):e465-e469.
174. Mair EA, Day RH. Cautery-assisted palatal stiffening operation. *Otolaryngol Head Neck Surg.* 2000;122(4):547-556.
175. Malow BA, Foldvary-Schaefer N, Vaughn BV, et al. Treating obstructive sleep apnea in adults with epilepsy: A randomized pilot trial. *Neurology.* 2008;71(8):572-577.
176. Mann RJ, Neaman KC, Armstrong SD, et al. The double-opposing buccal flap procedure for palatal lengthening. *Plast Reconstr Surg.* 2011;127(6):2413-2418.
177. Marcoux M. Home sleep diagnostics fall short of facility-based testing in MCAC's eyes. *Health News Daily.* 2004;16(190):1-2.
178. Martinho FL, Zonato AI, Bittencourt LR, Soares MC. Obese obstructive sleep apnea patients with tonsil hypertrophy submitted to tonsillectomy. *Brazil J Med Biol Res.* 2006;39(8):1137-1142.
179. Masood A, Phillips B. Radiofrequency ablation for sleep-disordered breathing. *Curr Opin Pulm Med.* 2001;7(6):404-406.
180. Massie CA, Hart RW, Peralez K, Richards GN. Effects of humidification on nasal symptoms and compliance in sleep apnea patients using continuous positive airway pressure. *Chest.* 1999;116(2):403-408.
181. McDaid C, Griffin S, Weatherly H, et al. Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea-hypopnoea syndrome: A systematic review and economic analysis. *Health Technol Assess.* 2009;13(4): 1-142.
182. McNicholas WT. Clinical diagnosis and assessment of obstructive sleep apnoea syndrome. *Monaldi Arch Chest Dis.* 1997;52(1):37-42.
183. Meoli AL, Rosen CL, Kristo D, et al. Nonprescription treatments of snoring or obstructive sleep apnea: An evaluation of products with limited scientific evidence. *Sleep.* 2003;26(5):619-624.

184. Mickelson SA, Rosenthal L. Midline glossectomy and epiglottidectomy for obstructive sleep apnea syndrome. *Laryngoscope*. 1997;107(5):614-619.
185. Miller SC, Nguyen SA, Ong AA, Gillespie MB. Transoral robotic base of tongue reduction for obstructive sleep apnea: A systematic review and meta-analysis. *Laryngoscope*. 2017;127(1):258-265.
186. Morgan CE, Johnson K. Snoring/obstructive sleep apnea, surgery. *eMedicine J* 2001;2(9). Available at: <http://www.emedicine.com/ent/topic370.htm>. Accessed January 18, 2002.
187. Morgenthaler TI, Aurora RN, Brown T, et al.; Standards of Practice Committee of the American Academy of Sleep Medicine (AASM). 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. *Sleep*. 2008;31(1):141-147.
188. Morgenthaler TI, Gay PC, Gordon N, et al. Adaptive servoventilation versus noninvasive positive pressure ventilation for central, mixed, and complex sleep apnea syndromes. *Sleep*. 2007;30(4):468-475.
189. Morgenthaler TI, Kapen S, Lee-Chiong T, et al; Standards of Practice Committee, American Academy of Sleep Medicine. Practice parameters for the medical therapy of obstructive sleep apnea. *Sleep*. 2006;29(8):1031-1035.
190. Morrell MJ, Meadows GE, Hastings P, et al. The effects of adaptive servo ventilation on cerebral vascular reactivity in patients with congestive heart failure and sleep-disordered breathing. *Sleep*. 2007;30(5):648-653.
191. Mundy L, Sullivan T, Merlin T, et al.; Horizon Scanning Unit, Adelaide Health Technology Assessment, University of Adelaide. The Pillar procedure: For the treatment of obstructive sleep apnoea and snoring. *Horizon Scanning Report*. Canberra, ACT: HealthPACT Secretariat, Department of Health and Ageing, Australian Government; September 2006. Available at: http://www.health.adelaide.edu.au/publichealth/research/horizon_scanning.html. Accessed January 29, 2007.
192. Murphey AW, Kandl JA, Nguyen SA, et al. The effect of glossectomy for obstructive sleep apnea: A systematic review and meta-analysis. *Otolaryngol Head Neck Surg*. 2015;153(3):334-342.

193. Mwenge GB, Rombaux P, Dury M, et al. Targeted hypoglossal neurostimulation for obstructive sleep apnoea. A 1 year pilot study. *Eur Respir J.* 2013;41(2):360-367.
194. Mwenge GB, Rombaux P, Lengele B, Rodenstein D. Hypoglossal nerve stimulation for obstructive sleep apnea. *Prog Neurol Surg.* 2015;29:94-105.
195. National Institute for Clinical Excellence (NICE). Radiofrequency ablation of the soft palate for snoring. Interventional Procedure Guidance No.124 . London, UK: NICE; May 2005.
196. National Institute for Health and Clinical Excellence (NICE). Soft palate implants for simple snoring. Interventional Procedure Guidance 240. London, UK: NICE; November 2007.
197. National Institute for Health and Clinical Excellence (NICE). Soft palate implants for obstructive sleep apnoea syndrome. Interventional Procedure Guidance 241. London, UK: NICE; November 2007.
198. National Institute for Health and Clinical Excellence (NICE). Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome. Technology Appraisal Guidance 139. London, UK: NICE; March 26, 2008.
199. Nelson LM. Combined temperature-controlled radiofrequency tongue reduction and UPPP in apnea surgery. *Ear Nose Throat J.* 2001;80(9):640-644.
200. NHIC Inc. Draft LCD for oral appliances for obstructive sleep apnea. LCD ID No. DL28603. Hingham, MA: NHIC; September 18, 2008.
201. NHIC, Corp. Respiratory assist devices. Local Coverage Determination (LCD) No. L11504. Durable Medical Equipment Medicare Administrative Carrier (DME MAC) Jurisdiction A. Hingham, MA: NHIC; revised March 13, 2008.
202. Nilius G, Happel A, Domanski U, Ruhle KH. Pressure-relief continuous positive airway pressure vs constant continuous positive airway pressure: A comparison of efficacy and compliance. *Chest.* 2006;130(4):1018-1024.
203. Nino-Murcia G, McCann CC, Blilwise DL, et al. Compliance and side effects in sleep apnea patients treated with nasal continuous positive airway pressure. *Western J Med.* 1989;150(2):165-169.
204. Nixon GM, Brouillette RT. Diagnostic techniques for obstructive sleep apnoea: Is polysomnography necessary? *Paediatr Respir Rev.* 2002;3(1):18-24.

205. Nordgard S, Hein G, Stene BK, et al. One-year results: Palatal implants for the treatment of obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2007;136(5):818-822.
206. Ohata K, Sakai E, Nakao T, et al. Efficacy of upper gastrointestinal endoscopic examination to identify patients with obstructive sleep apnea syndrome: A retrospective cross-sectional study. *Digestion.* 2019;99(3):252-259.
207. Oliven A. Treating obstructive sleep apnea with hypoglossal nerve stimulation. *Curr Opin Pulm Med.* 2011;17(6):419-424.
208. Olson LG, Ambrogetti A, Gyulay SG. Prediction of sleep-disordered breathing by unattended overnight oximetry. *J Sleep Res.* 1999;8(1):51-55.
209. Ong AA, Ayers CM, Kezirian EJ, et al. Application of drug-induced sleep endoscopy in patients treated with upper airway stimulation therapy. *World Journal of Otorhinolaryngology - Head and Neck Surgery.* 2017;3(2):92-96.
210. Ontario Ministry of Health and Long-Term Care, Medical Advisory Secretariat (MAS). Polysomnography in adults with obstructive sleep apnea. *Health Technology Policy Assessment.* Toronto, ON: MAS; June 2006.
211. OPAP Inc. Oral Pressure Appliance [website]. Capitola, CA: OPAP; October 31, 2001. Available at: <http://www.opap.com>. Accessed May 31, 2002.
212. OPAP Inc. Product labeling for OPAP Oral Pressure Appliance. Capitola, CA: OPAP; revised January 28, 2000. Available at: http://www.opap.com/fda_insert.htm. Accessed May 31, 2002.
213. Ozmen OA, Tüzemen G, Kasapoğlu F, et al. The reliability of SleepStrip as a screening test in obstructive sleep apnea syndrome. *Kulak Burun Bogaz Ihtis Derg.* 2011;21(1):15-19.
214. Pang KP, Dillard TA, Blanchard AR, et al. A comparison of polysomnography and the SleepStrip in the diagnosis of OSA. *Otolaryngol Head Neck Surg.* 2006;135(2):265-268.
215. Pang KP, Terris DJ. Modified cautery-assisted palatal stiffening operation: New method for treating snoring and mild obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2007;136(5):823-826.
216. Pang KP, Woodson BT. Expansion sphincter pharyngoplasty in the treatment of obstructive sleep apnea. *Oper Tech in Otolaryngol.* 2006;17:223-225.
217. Patel AV, Hwang D, Masdeu MJ, et al. Predictors of response to a nasal expiratory resistor device and its potential mechanisms of action for treatment of obstructive sleep

- apnea. *J Clin Sleep Med.* 2011;7(1):13-22.
218. Patel SR, White DP, Malhotra A, et al. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive apnea. *Arch Internal Med.* 2003;163:565-571.
219. Pau MC, Zinelli E, Fois SS, et al. Circulating malondialdehyde concentrations in obstructive sleep apnea (OSA): A systematic review and meta-analysis with meta-regression. *Antioxidants (Basel).* 2021;10(7):1053.
220. Pazos G, Mair EA. Complications of radiofrequency ablation in the treatment of sleep-disordered breathing. *Otolaryngol Head Neck Surg.* 2001;125(5):462-467.
221. Pensler JM, Reich DS. A comparison of speech results after the pharyngeal flap and the dynamic sphincteroplasty procedures. *Ann Plast Surg.* 1991;26(5):441-443.
222. Pepin JL, Chouri-Pontarollo N, Tamisier R, et al. Cheyne-Stokes respiration with central sleep apnoea in chronic heart failure: Proposals for a diagnostic and therapeutic strategy. *Sleep Med Rev.* 2006;10(1):33-47.
223. Pepin JL, Defaye P, Garrigue S, Overdrive atrial pacing does not improve obstructive sleep apnoea syndrome. *Eur Respir J.* 2005;25(2):343-347.
224. Pepin JL, Krieger J, Rodenstein D, et al. Effective compliance during the first 3 months of continuous positive airway pressure treatment. A European prospective study of 121 patients. *Am J Respir Crit Care Med.* 1999;160(4):1124-1129.
225. Pepperell JC, Maskell NA, Jones DR, et al. A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. *Am J Respir Crit Care Med.* 2003;168(9):1109-1114.
226. Permut I, Montserrat D, Wissam C, et al. Comparison of positional therapy to CPAP in patients with positional obstructive sleep apnea. *J Clin Sleep Med.* 2010;6(3):238-243.
227. Philip P, Heiser C, Bioulac S, et al. Hypoglossal nerve stimulation on sleep and level of alertness in OSA: A preliminary study. *Neurology.* 2018;91(7):e615-e619.
228. Picavet VA, Dellian M, Gehrking E, et al. Treatment of snoring using a non-invasive Er:YAG laser with SMOOTH mode (NightLase): A randomized controlled trial. *Eur Arch Otorhinolaryngol.* 2022 Jul 22 [Online ahead of print].
229. Pichon Riviere A, Augustovski F, Alcaraz A, et al. Outpatient BiPAP (bi-level positive airway pressure) in obstructive sleep apnea. Technology Assessment. Buenos Aires, Argentina; Institute for Clinical Effectiveness and Health Policy (IECS); January 2006.

230. Powell NB, Riley RW, Guilleminault C. Radiofrequency tongue base reduction in sleep-disordered breathing: A pilot study. *Otolaryngol Head Neck Surg.* 1999;120(5):656-664.
231. Powell NB, Riley RW, Troell RJ, et al. Radiofrequency volumetric reduction of the tongue. A porcine pilot study for the treatment of obstructive sleep apnea syndrome. *Chest.* 1997;111(5):1348-1355.
232. Rakotonanahary D, Pelletier-Fleury N, Gagnadoux F, Fleury B. Predictive factors for the need for additional humidification during nasal continuous positive airway pressure therapy. *Chest.* 2001;119(2):460-465.
233. Ramachandran SK, Josephs LA. A meta-analysis of clinical screening tests for obstructive sleep apnea. *Anesthesiology.* 2009;110(4):928-939.
234. Ramar K, Dort LC, Katz SG, et al. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: An update for 2015. *J Clin Sleep Med.* 2015;11(7):773-827.
235. Randerath W, Bauer M, Blau A, et al; Taskforce der Arbeitsgruppe Apnoe der DGSM. Are there alternative therapeutical options other than CPAP in the treatment of the obstructive sleep apnea syndrome? *Pneumologie.* 2007;61(7):458-466.
236. Randerath WJ, Verbraecken J, Andreas S, et al; European Respiratory Society task force on non-CPAP therapies in sleep apnoea. Non-CPAP therapies in obstructive sleep apnoea. *Eur Respir J.* 2011;37(5):1000-1028. Available at: <http://www.ers-education.org/media/2011/pdf/156487.pdf>. Accessed January 3, 2012.
237. Randerath WJ, Verbraecken J, Andreas S, et al; European Respiratory Society task force on non-CPAP therapies in sleep apnoea. Non-CPAP therapies in obstructive sleep apnoea. *Eur Respir J.* 2011;37(5):1000-1028.
238. Ratneswaran D, Guni A, Pengo MF, et al. Electrical stimulation as a therapeutic approach in obstructive sleep apnea -- a meta-analysis. *Sleep Breath.* 2021;25(1):207-218
239. Ravesloot MJL, White D, Heinzer R, et al. Efficacy of the new generation of devices for positional therapy for patients with positional obstructive sleep apnea: A systematic review of the literature and meta-analysis. *J Clin Sleep Med.* 2017;13(6):813-824.
240. Restore Medical, Inc. Simple, effective treatment for sleep apnea and snoring. Announcing a breakthrough treatment for sleep-related breathing disorders-the Pillar® Procedure from Restore Medical [website]. St. Paul, MN: Restore Medical; 2004. Available at: <http://www.restoremedical.com>. Accessed December 21, 2004.

241. Riley RW, Powell NB, Guilleminault C. Inferior mandibular osteotomy and hyoid myotomy suspension for obstructive sleep apnea. A review of 55 patients. *J Oral Maxillofac Surg.* 1989;47:159-164.
242. Riley RW, Powell NB, Guilleminault C. Inferior sagittal osteotomy of the mandible with hyoid myomotomy suspension: A new procedure for obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 1986;84:589.
243. Riley RW, Powell NB, Guilleminault C. Maxillary mandibular and hyoid advancement for treatment of obstructive sleep apnea. A review of 40 patients. *J Oral Maxillofac Surg.* 1990;48:20-26.
244. Rolfe I, Olson LG, Saunders NA. Long-term acceptance of continuous airway pressure in obstructive sleep apnea. *Am Rev Respir Dis.* 1991;144(5):1130-1133.
245. Rosen IM, Kirsch DB, Chervin RD, et al; American Academy of Sleep Medicine Board of Directors. Clinical use of a home sleep apnea test: An American Academy of Sleep Medicine position statement. *J Clin Sleep Med.* 2017;13(10):1205-1207.
246. Rosenthal L, Massie CA, Dolan DC, et al. A multicenter, prospective study of a novel nasal EPAP device in the treatment of obstructive sleep apnea: Efficacy and 30-day adherence. *J Clin Sleep Med.* 2009;5(6):532-537.
247. Ryan PJ, Hilton MF, Boldy DA, et al. Validation of British Thoracic Society guidelines for the diagnosis of the sleep apnoea/hypopnoea syndrome: Can polysomnography be avoided? *Thorax.* 1995;50(9):972-975.
248. Schmidt-Nowara W, Lowe A, Wiegand L, et al. Oral appliances for the treatment of snoring and obstructive sleep apnea: An American Sleep Disorders Association Review. *Sleep.* 1995;18(6):501-510.
249. Schulz R, Mahmoudi S, Hattar K, et al. Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Impact of continuous positive airway pressure therapy. *Am J Respir Crit Care Med.* 2000;162(2 Pt 1):566-570.
250. Schwab RJ. Upper airway imaging in obstructive sleep apnea in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed August 2016.
251. Series F, Marc I, Cormier Y, et al. Utility of nocturnal home oximetry for case finding in patients with suspected sleep apnea hypopnea syndrome. *Ann Intern Med.* 1993;119:449-453.

252. Series F. Accuracy of an unattended home CPAP titration in the treatment of obstructive sleep apnea. *Am J Respir Crit Care Med.* 2000;162(1):94-97.
253. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep.* 1996;19(2):156-177.
254. Sher AE. Update on upper airway surgery for obstructive sleep apnea. *Curr Opin Pulm Med.* 1995;1(6):504-511.
255. Shi Y, Chen L, Chen T, et al. A meta-analysis of voxel-based brain morphometry studies in obstructive sleep apnea. *Sci Rep.* 2017;7(1):10095.
256. Shiffman HS, Khorsandi J, Cauwels NM, et al. Minimally invasive combined Nd:YAG and Er:YAG laser-assisted uvulopalatoplasty for treatment of obstructive sleep apnea. *Photobiomodul Photomed Laser Surg.* 2021;39(8):550-557.
257. Shneerson J, Wright J. Lifestyle modification for obstructive sleep apnoea. *Cochrane Database Syst Rev.* 2001;(1):CD002875.
258. Signifier Medical Technologies, LLC. Efficacy of intra-oral neuromuscular stimulation training on snoring and mild sleep apnoea. ClinicalTrials.gov Identifier: NCT04392765. Bethesda, MD: National Library of Medicine; updated February 11, 2022.
259. Signifier Medical Technologies, LLC. eXciteOSA user guide. Boston, MA: Signifier Medical Technologies; 2021. Available at: https://exciteosa.com/wp-content/uploads/2021/03/User_Guide.pdf. Accessed April 4, 2022.
260. Signifier Medical Technologies, LLC. Signifier Medical ushers in new era of treatment for sleep apnea and snoring with FDA approval of eXciteOSA device. Press Release: Business Wire [online]. Boston, MA: Signifier Medical Technologies; February 8, 2021.
261. Simantirakis EN, Schiza SE, Chrysostomakis SI, et al. Atrial overdrive pacing for the obstructive sleep apnea-hypopnea syndrome. *N Engl J Med.* 2005;353(24):2568-2577.
262. Skinner MA, Kingshott RN, Filsell S, et al. Efficacy of the 'tennis ball technique' versus nCPAP in the management of position-dependent obstructive sleep apnea syndrome. *Respirology.* 2008;13(5):708-715.
263. Smith I, Lasserson TJ, Wright J. Drug therapy for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev.* 2006;(2):CD003002.
264. Smith I, Lasserson TJ. Pressure modification for improving usage of continuous positive airway pressure machines in adults with obstructive sleep apnoea. *Cochrane Database Syst Rev.* 2009;(4):CD003531.

265. Smith I, Nadig V, Lasserson TJ. Educational, supportive and behavioural interventions to improve usage of continuous positive airway pressure machines for adults with obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2009;(2): CD007736.
266. Soares D, Sinawe H, Folbe AJ, et al. Lateral oropharyngeal wall and supraglottic airway collapse associated with failure in sleep apnea surgery. *Laryngoscope*. 2012;122(2):473-479.
267. Song SA, Chang ET, Cortal V, et al. Genial tubercle advancement and genioplasty for obstructive sleep apnea: A systematic review and meta-analysis. *Laryngoscope*. 2017;127(4):984-992.
268. Soose RJ, Woodson BT, Gillespie MB, et al, STAR Trial Investigators. Upper airway stimulation for obstructive sleep apnea: Self-reported outcomes at 24 months. *J Clin Sleep Med* 2016;12(1):43-48.
269. Srijithesh PR, Aghoram R, Goel A, Dhanya J. Positional therapy for obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2019;5:CD010990.
270. Steffen A, Sommer JU, Hofauer B, et al. Outcome after one year of upper airway stimulation for obstructive sleep apnea in a multicenter German post-market study. *Laryngoscope*. 2018;128(2):509-515.
271. Steward DL, Huntley TC, Woodson BT, Surdulescu V. Palate implants for obstructive sleep apnea: Multi-institution, randomized, placebo-controlled study. *Otolaryngol Head Neck Surg*. 2008;139(4):506-510.
272. Stoohs R, Guilleminault C. MESAM 4: An ambulatory device for the detection of patients at risk for obstructive sleep apnea. *Chest*. 1992;101(5):1221-1227.
273. Strohl KP. Overview of obstructive sleep apnea in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed November 2014.
274. Strohl KP. Overview of obstructive sleep apnea in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed November 2015.
275. Strohl KP. Overview of obstructive sleep apnea in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed August 2016.
276. Strollo PJ Jr, Gillespie MB, Soose RJ, et al.; Stimulation Therapy for Apnea Reduction (STAR) Trial Group.. Upper airway stimulation for obstructive sleep apnea: Durability of the treatment effect at 18 months. *Sleep*. 2015;38(10):1593-8.

277. Strollo PJ Jr, Soose RJ, Maurer JT, et al; STAR Trial Group. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med.* 2014;370(2):139-149.
278. Stuck BA, Maurer JT, Hormann K. Tongue base reduction with radiofrequency tissue ablation: Preliminary results after two treatment sessions. *Sleep Breath.* 2000;4(4):155-162.
279. Stuck BA, Maurer JT, Verse T, Hormann K. Tongue base reduction with temperature-controlled radiofrequency volumetric tissue reduction for treatment of obstructive sleep apnea syndrome. *Acta Otolaryngol.* 2002;122(5):531-536.
280. Suh GD. Evaluation of open midline glossectomy in the multilevel surgical management of obstructive sleep apnea syndrome. *Otolaryngol Head Neck Surg.* 2013;148(1):166-171.
281. Sundaram S, Bridgman SA, Lim J, Lasserson TJ. Surgery for obstructive sleep apnoea. *Cochrane Database Syst Rev.* 2005;(4): CD001004..
282. Swedish Council on Technology Assessment in Healthcare (SBU). Obstructive sleep apnoea syndrome - Report of a joint Nordic project. A systematic literature review. SBU Report 184E. Stockholm, Sweden: SBU; 2007.
283. Szollosi I, O'Driscoll DM, Dwyer MJ, et al. Adaptive servo-ventilation and deadspace: Effects on central sleep apnoea. *J Sleep Res.* 2006;15(2):199-205.
284. Teberik K, Eski MT, Balbay EG, Kaya M. Evaluation of intraocular pressure, corneal thickness, and retinal nerve fiber layer thickness in patients with obstructive sleep apnea syndrome. *Pak J Med Sci.* 2018;34(4):817-822.
285. Terris DJ, Chen V. Occult mucosal injuries with radiofrequency ablation of the palate. *Otolaryngol Head Neck Surg.* 2001;125(5):468-472.
286. Teschler H, Dohring J, Wang YM, et al. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. *Am J Respir Crit Care Med.* 2001;164(4):614-619.
287. Teschler H, Stamp JW, Farhat AA, et al. Comparison of the efficacy of BiPAP-S/T and the VPAP-S/T ventilators in patients with stable chronic respiratory insufficiency. *Pneumologie.* 1998;52(6):305-310.
288. Thaler ER, Schwab RJ. Single-institution experience and learning curve with upper airway stimulation. *Laryngoscope.* 2016;126 Suppl 7:S17-S19.

289. Thomas AJ, Chavoya M, Terris DJ. Preliminary findings from a prospective, randomized trial of two tongue-base surgeries for sleep-disordered breathing. *Otolaryngol Head Neck Surg.* 2003;129(5):539-546.
290. Thorpy MJ. The clinical use of the multiple sleep latency test. Standards of Practice Committee of the American Sleep Disorders Association Report. *Sleep.* 1992;15(3):268-276.
291. Tice JA. Portable devices for home testing for obstructive sleep apnea. Technology Assessment. San Francisco, CA: California Technology Assessment Forum (CTAF); June 15, 2005.
292. Tice JA. Portable devices in home testing for obstructive sleep apnea. A Technology Assessment. San Francisco, CA: California Technology Assessment Forum (CTAF); 2009.
293. Toh ST, Han HJ, Tay HN, Kiong KL. Transoral robotic surgery for obstructive sleep apnea in Asian patients: A Singapore sleep centre experience. *JAMA Otolaryngol Head Neck Surg.* 2014;140(7):624-629.
294. Topfer V, El-Sebai M, Wessendorf TE, et al. [Adaptive servoventilation: Effect on Cheyne-Stokes-Respiration and on quality of life]. *Pneumologie.* 2004;58(1):28-32.
295. Trikalinos TA, Ip S, Raman G, et al. Home diagnosis of obstructive sleep apnea-hypopnea syndrome. Technology Assessment. Prepared for AHRQ by the Tufts-New England Medical Center Evidence-based Practice Center. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); August 8, 2007.
296. Trikalinos TA, Lau J. Obstructive sleep apnea-hypopnea syndrome: Modeling different diagnostic strategies. Technology Assessment. Prepared for AHRQ by the Tufts-New England Medical Center Evidence-based Practice Center. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); December 4, 2007.
297. Troell RJ, Riley RW, Powell NB, et al. Surgical management of the hypopharyngeal airway in sleep disordered breathing. *Otolaryngol Clin North Am.* 1998;31(6):979-1012.
298. Tsui WK, Yang Y, Cheung LK, Leung YY. Distraction osteogenesis as a treatment of obstructive sleep apnea syndrome: A systematic review. *Medicine (Baltimore).* 2016;95(36):e4674.
299. Tun Y, Hida W, Okabe S, et al. Effects of nasal continuous positive airway pressure on awake ventilatory responses to hypoxia and hypercapnia in patients with obstructive sleep apnea. *Tohoku J Exp Med.* 2000;190(2):157-168.

300. U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services (CMS). Continuous positive airway pressure (CPAP). Medicare Coverage Issues Manual §60-17. Baltimore, MD: CMS; 2002.
301. U.S. Department of Health and Human Services, Centers for Medicare and Medicaid Services (CMS). Decision memo for continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea (OSA) (CAG-0093R2). Medicare Coverage Database. Baltimore, MD: CMS; March 13, 2008.
302. U.S. Department of Health and Human Services, National Institutes of Health (NIH), National Heart, Lung and Blood Institute (NHLBI). Sleep apnea: Is your patient at risk? NIH Pub. No. 95-3803. Bethesda, MD: NIH; September 1995.
303. U.S. Food and Drug Administration (FDA), Center for Devices and Radiologic Health (CDRH). Pillar™ Palatal Implant System. 510(k) no. K040417. Rockville, MD: FDA; July 28, 2004.
304. U.S. Food and Drug Administration (FDA). FDA authorizes marketing of novel device to reduce snoring and mild obstructive sleep apnea in patients 18 years and older. FDA News Release. Silver Spring, MD: FDA; February 5, 2021.
305. U.S. Food and Drug Administration (FDA). Implantable upper airway stimulation for obstructive sleep apnea. Inspire upper airway stimulation (UAS). Summary of Safety and Effectiveness Data. Premarket Approval Application (PMA) No. P130008. Silver Spring, MD: FDA; April 30, 2014.
306. U.S. Food and Drug Administration (FDA). Inspire Upper Airway Stimulation - P130008/S089. Silver Spring, MD: FDA; March 20, 2023.
307. U.S. Food and Drug Administration (FDA). Zzoma Positional Sleeper. 510(k) No. K100160. Rockville, MD: FDA; May 11, 2010.
308. U.S. Food and Drug Administration (FDA). Inspire II Upper Airway Stimulator. Premarket Approval (PMA) Supplement No. S021. Silver Spring, MD: FDA; March 29, 2017.
309. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for obstructive sleep apnea in adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2017;317(4):407-414.
310. Valbuza JS, de Oliveira MM, Conti CF, et al. Methods for increasing upper airway muscle tonus in treating obstructive sleep apnea: Systematic review. Sleep Breath. 2010;14(4):299-305.

311. Van de Heyning PH, Badr MS, Baskin JZ, et al. Implanted upper airway stimulation device for obstructive sleep apnea. *Laryngoscope*. 2012;122(7):1626-1633.
312. Van den Bossche K, Van de Perck E, Kazemeini E, et al. Natural sleep endoscopy in obstructive sleep apnea: A systematic review. *Sleep Med Rev*. 2021;60:101534.
313. van Maamen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the Sleep Position Trainer in the treatment of positional obstructive sleep apnea syndrome. *Sleep*. 2014;37(7):1209-1215.
314. Vanderveken OM, Devolder A, Marklund M, et al. Comparison of a custom-made and a thermoplastic oral appliance for the treatment of mild sleep apnea. *Am J Respir Crit Care Med*. 2008;178(2):197-202.
315. Varvarigou V, Dahabreh IJ, Malhotra A, Kales SN. A review of genetic association studies of obstructive sleep apnea: Field synopsis and meta-analysis. *Sleep*. 2011;34(11):1461-1468.
316. Verse T, Kroker BA, Pirsig W, Brosch S. Tonsillectomy as a treatment of obstructive sleep apnea in adults with tonsillar hypertrophy. *Laryngoscope*. 2000;110(9):1556-1559.
317. Vicini C, Montevercchi F, Gobbi R, et al. Transoral robotic surgery for obstructive sleep apnea syndrome: Principles and technique. *World J Otorhinolaryngol Head Neck Surg*. 2017;3(2):97-100.
318. Volner K, Chao S, Camacho M, et al. Dynamic sleep MRI in obstructive sleep apnea: A systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. 2022;279(2):595-607.
319. Volner K, Dunn B, Chang ET, et al. Transpalatal advancement pharyngoplasty for obstructive sleep apnea: A systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. 2017;274(3):1197-1203.
320. Waeckerle JF, Smith HA, McNabney WK. Hereditary angioneurotic edema treated by partial uvulectomy. *JACEP*. 1976;5(6):446-448.
321. Waldhorn RE, Herrick TW, Nguyen MC, et al. Long-term compliance with nasal continuous positive airway pressure therapy of obstructive sleep apnea. *Chest*. 1990;97(1):33-38.
322. Walker RP, Levine HL, Hopp ML, Greene D. Extended follow-up of palatal implants for OSA treatment. *Otolaryngol Head Neck Surg*. 2007;137(5):822-827.
323. Walsh JK, Griffin KS, Forst EH, et al. A convenient expiratory positive airway pressure nasal device for the treatment of sleep apnea in patients non-adherent with continuous

- positive airway pressure. *Sleep Med.* 2011;12(2):147-152.
324. Wang W, He M, Huang W. Changes of retinal nerve fiber layer thickness in obstructive sleep apnea syndrome: A systematic review and meta-analysis. *Curr Eye Res.* 2017;42(5):796-802.
325. Wassmuth Z, Mair E, Loube D, Leonard D. Cautery-assisted palatal stiffening operation for the treatment of obstructive sleep apnea syndrome. *Otolaryngol Head Neck Surg.* 2000;123(1 Pt 1):55-60.
326. Weaver EM, Kapur VK. Surgical treatment of obstruction sleep apnea in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed April 2017; January 2021.
327. Woodson BT, Derowe A, Hawke M, et al. Pharyngeal suspension suture with repose bone screw for obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2000;122(3):395-401.
328. Woodson BT, Gillespie MB, Soose RJ, et al; STAR Trial Investigators. Randomized controlled withdrawal study of upper airway stimulation on OSA: Short- and long-term effect. *Otolaryngol Head Neck Surg.* 2014;151(5):880-887.
329. Woodson BT, Nelson L, Mickelson S, et al. A multi-institutional study of radiofrequency volumetric tissue reduction for OSAS. *Otolaryngol Head Neck Surg.* 2001;125(4):303-311.
330. Woodson BT, Soose RJ, Gillespie MB. Three-year outcomes of cranial nerve stimulation for obstructive sleep apnea: The STAR Trial. *Otolaryngol Head Neck Surg.* 2016;154(1):181-188.
331. Woodson BT, Steward DL, Mickelson S, et al. Multicenter study of a novel adjustable tongue-advancement device for obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2010;143(4):585-590.
332. Woodson BT, Steward DL, Weaver EM, et al. A randomized trial of temperature-controlled radiofrequency, continuous positive airway pressure, and placebo for obstructive sleep apnea syndrome. *Otolaryngol Head Neck Surg.* 2003;128(6):848-861.
333. Woodson BT, Strohl KP, Soose RJ, et al. Upper airway stimulation for obstructive sleep apnea: 5-year outcomes. *Otolaryngol Head Neck Surg.* 2018;159(1):194-202.
334. Woodson BT. Transpalatal advancement pharyngoplasty outcomes compared with uvulopalatopharyngoplasty. *Otolaryngol Head Neck Surg.* 2005;133(2):211-217.
335. Wright J, Johns R, Watt I, et al. Health effects of obstructive sleep apnea and the effectiveness of continuous positive airways pressure: A systematic review of the

research evidence. BMJ. 1997;314(7084):851-860.

336. Wu X, She W, Niu X, Chen X. Association between serum level of advanced glycation end products and obstructive sleep apnea-hypopnea syndrome: A meta-analysis. J Int Med Res. 2018;46(11):4377-4385.
337. Xu H, Qian Y, Guan J, et al. No association between the ApoE ε2 and ε4 alleles and the risk of obstructive sleep apnea: A systematic review and meta-analysis. Biomed Rep. 2015;3(3):313-318.
338. Yadollahi A, Montazeri A, Azarbarzin A, Moussavi Z. Respiratory flow-sound relationship during both wakefulness and sleep and its variation in relation to sleep apnea. Ann Biomed Eng. 2013;41(3):537-546.
339. Yanagisawa-Minami A, Sugiyama T, Iwasaki T, Yamasaki Y. Primary site identification in children with obstructive sleep apnea by computational fluid dynamics analysis of the upper airway. J Clin Sleep Med. 2020;16(3):431-439.
340. Zapanta PE. Sleep endoscopy. Medscape. January 3, 2018. Available at: <https://emedicine.medscape.com/article/1963060-overview#a3>. Accessed May 9, 2018.
341. Zhang XL, Yin KS, Li XL, et al. Efficacy of adaptive servoventilation in patients with congestive heart failure and Cheyne-Stokes respiration. Chin Med J (Engl). 2006;119(8):622-627.
342. Zhong A, Xiong X, Xu H, Shi M. An updated meta-analysis of the association between tumor necrosis factor-α -308G/A polymorphism and obstructive sleep apnea-hypopnea syndrome. PLoS One. 2014;9(9):e106270.



Copyright Aetna Inc. All rights reserved. Clinical Policy Bulletins are developed by Aetna to assist in administering plan benefits and constitute neither offers of coverage nor medical advice. This Clinical Policy Bulletin contains only a partial, general description of plan or program benefits and does not constitute a contract. Aetna does not provide health care services and, therefore, cannot guarantee any results or outcomes. Participating providers are independent contractors in private practice and are neither employees nor agents of Aetna or its affiliates. Treating providers are solely responsible for medical advice and treatment of members. This Clinical Policy Bulletin may be updated and therefore is subject to change.

Copyright © 2001-2024 Aetna Inc.

[Language services can be provided by calling the number on your member ID card. For additional language assistance:](#) [Español](#) | [中文](#) | [Tiếng Việt](#) | [한국어](#) | [Tagalog](#) | [Русский](#) | [العربية](#) | [Kreyòl](#) | [Français](#) | [Polski](#) | [Português](#) | [Italiano](#) | [Deutsch](#) | [日本語](#) | [فارسی](#) | [Other Languages...](#) | [↗](http://www.aetna.com/individuals-families/contact-aetna/information-in-other-languages.html) (<http://www.aetna.com/individuals-families/contact-aetna/information-in-other-languages.html>)