Treatment of Obstructive Sleep Apnea*

A Review

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Treatment of obstructive sleep apnea (OSA) has developed over the last 25 years from tracheostomy to a variety of options, including weight loss, nasal continuous positive airway pressure (N-CPAP), pharyngeal surgery, and medications. None of these options is definitive or curative, except possibly weight loss. The most widely prescribed treatment is N-CPAP, but recently published studies using objective measurement of patient compliance show less than ideal compliance. Attempts have been made to design pharyngeal surgery according to the site of upper airway collapse or narrowing, as identified by various techniques in wakefulness. How representative these studies are of upper airway physiology in sleep is questionable. Recent studies have shown improved surgical success in correcting OSA. However, disturbing data are available in a limited number of patients that demonstrate worsening of the OSA months after a favorable response to surgery. More studies assessing the long-term outcome of pharyngeal surgery are needed. Several pharmacologic agents have been used to treat OSA. Results with any particular agent are not better than with N-CPAP or surgery. However, studies of subgroups of patients with OSA in which a particular pharmacologic agent may be specifically indicated, such as thyroxine in hypothyroidism, have not been conducted (to our knowledge). An algorithm for the approach to treatment recommendations is presented. Basic to this algorithm is an objective presentation of therapeutic options to the patient with OSA and a respect for the patient’s preferences.

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Key words: N-CPAP; sleep apnea; upper airway; uvulopalatopharyngoplasty

Abbreviations: AHI=apnea/hypopnea index; N-CPAP=nasal-continuous positive airway pressure; OSA=obstructive sleep apnea; REM=rapid eye movement; UPPP=uvulopalatopharyngoplasty

Our awareness of the clinical importance of obstructive sleep apnea (OSA) has existed for 25 to 30 years. Although the prevalence of this disease and its health consequences are still under study, it is apparent from the data of He et al that significant morbidity and mortality are associated with OSA, even for those younger than 50 years of age. Preliminary evidence suggests that patients with OSA have an increased susceptibility to cardiovascular complications such as hypertension, cardiac arrhythmias, stroke, and myocardial infarction. A possible common mechanism for these adverse outcomes is increased sympathetic nervous system activity, known to be present in patients with OSA. Most likely, hypoxemia present in sleep in patients with OSA contributes to this increased sympathetic nervous system stimulation and to its adverse consequences. Whether OSA is an independent risk factor for cardiovascular disease separate from obesity, hypertension, and diabetes is currently under investigation by a National Institutes of Health-sponsored, multicenter, prospective study.

Excessive daytime sleepiness also is a major complication of OSA. Impairment of alertness may make one susceptible to work or driving accidents and/or to poor work and social functioning. Thus, the rationale for treatment of OSA is based on the following: (1) susceptibility of patients with OSA to major cardiovascular illness and hypoxic complications, and (2) the consequences of excessive daytime sleepiness.

The purpose of this article is to review the results of therapies utilized to date to treat OSA. Categories to be discussed are as follows: weight loss, nasal-
continuous positive airway pressure, (N-CPAP), pharyngeal surgery, and pharmacologic treatment. Following this review, a recommended practical therapeutic approach to the patient with OSA will be presented.

**Weight Loss**

Obesity has been known to be a common clinical characteristic of patients with OSA for some time.\(^{14-18}\) Both anatomic and physiologic abnormalities may exist because of obesity in patients with OSA. More recent investigations demonstrate that body fat tends to be distributed in the upper body in patients with OSA, such that neck obesity and pharyngeal fat deposition may be important.\(^{19,20}\) Shelton et al\(^{20}\) found a correlation between the severity of OSA and the volume of pharyngeal adipose tissue, as detected by MRI. In two patients studied after weight loss and improvement in the OSA, these investigators found that the volume of pharyngeal fat had decreased. Weight loss also has been associated with an improvement in upper airway function. Suratt et al\(^{19}\) found less pharyngeal collapsibility in patients with OSA after weight loss; and Rubinstein et al\(^{21}\) found an increase in the pharyngeal airway cross-sectional area, as measured by acoustic reflection, in OSA patients following weight loss.

Weight loss is quite effective in decreasing the number of apneic events, the extent of arterial oxygen desaturation, and the amount of sleep disruption seen in patients with OSA.\(^{14,22}\) It has been noted that the relationship between weight loss and improvement in the number of apneas and hypopneas is not linear,\(^{14}\) in that a large improvement in OSA can occur with rather minimal weight loss. The number of apneas will decrease by approximately 50% with a 10% weight loss. This fact should be used in encouraging OSA patients at least to lose some weight. Harder than losing weight initially is keeping it off. Behavioral modification, combined with long-term follow-up, has been shown to be effective in aiding weight loss maintenance, at least in nonapneic obese populations.\(^{23,24}\) Hopefully, OSA patients would be amenable to this type of counseling.

Weight reduction surgery has been used in obese OSA patients.\(^{25-27}\) In a very interesting series, Sugarman et al\(^{27}\) showed that gastric reduction or bypass surgery was quite effective in treating obese individuals with sleep-related alveolar hypventilation (pickwickian syndrome), those with OSA, or patients with a combination of both. Patients who had a polysomnogram following surgery had a mean weight loss of 57 kg, a decrease of 32% from their initial weight. The apnea/hypopnea index (AHI) (number of abnormal breathing events per hour of sleep) improved from a mean value of 64 to 26. Cardiac and respiratory functions were also shown to improve in these patients. Symptomatic benefit and weight loss persisted for at least two thirds of 57 OSA patients who could be located 4.5 years following surgery. However, polysomnograms were not performed at this time. Unfortunately, but as might have been anticipated, the operative mortality for these obese OSA patients with respiratory insufficiency was higher than in those obese subjects without respiratory failure who underwent the same procedure. This factor must be considered when discussing such therapy with OSA patients.

From review of this literature, weight loss has to be considered as a very helpful therapy for most patients with OSA. Therefore, weight loss should receive a major focus in our therapeutic planning and discussions with OSA patients. Surely, dietary counseling and regular follow-up provided by a nutritional consultant should be strongly advised for the overweight OSA patient. If patients are resistant or noncompliant with a weight loss program, psychiatric consultation may be helpful. In such individuals, surgery for weight loss should be considered, realizing that the operative procedure alone will not ensure weight loss since by eating more frequently, one can sabotage the purpose of weight loss surgery. Again psychiatric therapy may be helpful here.

**Nasal-Continuous Positive Airway Pressure**

By producing a positive pressure within the upper airway to counteract the subatmospheric collapsing pharyngeal pressure produced during an obstructive apnea, N-CPAP is an effective treatment for OSA. However, the success of N-CPAP is hampered by poor compliance by many OSA patients. It is not hard to understand why wearing a cumbersome facemask throughout sleep every night would be difficult. However, since nearly all patients can tolerate N-CPAP beyond the sleep laboratory (85 to 92% of patients\(^{28}\)), and since nearly all notice a beneficial effect of this device, poor compliance becomes somewhat more difficult to understand. In addition to the noise and cumbersome nature of the N-CPAP compressors (variables on which industry continues to improve), a high percentage of OSA patients complain of nasal or oral dryness, nasal congestion, sneezing, sinusitis, nose bleeds, and/or rhinorrhea.\(^{29,30}\) Skin reactions from the facemask, nasal bridge abrasions, red eyes, and aerophagia are commonly reported.\(^{29,30}\) In these studies, nasal dryness was observed more frequently in those with more serious OSA, but the severity of the OSA was not a factor in the presence of other side effects. Humidification of the N-CPAP system or the level of N-CPAP required did not influence the presence of these symptoms.\(^{30}\)

The success of N-CPAP treatment is directly dependent on the patient’s willingness to wear the device.
Earlier studies of N-CPAP compliance, based on patient report, demonstrated very good compliance.\textsuperscript{28,31,32} More recent studies using built-in timers on the N-CPAP compressors or pressure sensors within the mask that determine the hours of N-CPAP use have not confirmed such good compliance.\textsuperscript{33-37} The average nightly use of N-CPAP reported was close to 5 h in 4 studies,\textsuperscript{33-35,37} but was 6 h in 1 study.\textsuperscript{36} However, in a study using a microprocessor to record continuous time, only 46% of the 35 patients studied were shown to have used the N-CPAP for at least 4 h on 70% of nights.\textsuperscript{35} In fact, only two patients in this group used the N-CPAP for 7 or more hours on 70% of the nights. Interestingly, compliance was no better with bilevel pressure application than with continuous pressure.\textsuperscript{37}

Examination of factors that might predict N-CPAP compliance has been conducted. Severity of disease and the level of N-CPAP required to control the OSA were not always helpful; the level of education and the degree of improvement sensed by the patient after N-CPAP use appeared to be variables that may be predictive of long-term good N-CPAP compliance.\textsuperscript{35,36} Thus, better-educated individuals with more severe disease likely will use their N-CPAP more regularly than those with a low level of education and/or less severe disease. Other forms of treatment may be more appropriate for the latter group of patients.

The primary benefit of N-CPAP is that it does improve survival in patients with OSA relative to the results of conservative therapy of weight loss recommendations.\textsuperscript{4,38} Results differ in the two studies examining the effect of pharyngeal surgery on survival. He et al\textsuperscript{38} did not find that this surgery improved outcome, while Kennan et al\textsuperscript{48} showed that uvulopalatopharyngoplasty (UPPP) outcome was equivalent to that of N-CPAP over a 6-year period. However, even in this study, there were more cardiovascular deaths in the UPPP-treated patients than in the N-CPAP-treated patients. Thus, it seems logical to recommend N-CPAP in adults with severe OSA along with weight loss, if the latter is needed, except for those with significant upper airway anatomic abnormalities, in whom pharyngeal surgery may be helpful. However, because of loss of control of OSA in some patients postsurgically, it is important to follow up these patients for several years after their pharyngeal surgery.

Pharyngeal Surgery

Several operative procedures have been developed for the treatment of OSA. Although it would be ideal to recommend the procedure of choice to a given patient based on a characterization of the upper airway anatomy and/or physiology, information supporting this approach is not yet available. This presentation will discuss what is known about (1) site of upper airway obstruction, (2) prediction of surgical success by site of obstruction identification, and (3) operative procedures available.

Site of Upper Airway Obstruction

In the 1980s, several studies were performed in an attempt to identify the specific pharyngeal site of obstruction in OSA. These studies used different techniques: fluoroscopy, CT, cephalometry, upper airway pressure measurements, and direct visualization to examine the anatomy of the upper airway in patients with OSA. Most of these evaluations were done with the patient awake and some were done with the patient sitting. Therefore, the relevance of the results of such studies to events that occur with the patient asleep and lying down has to be questioned. Several studies using standard, cine, or ultrafast CT scans have shown narrowing or collapse of primarily the retropalatal airway, but also of the hypopharynx.\textsuperscript{39-45} Cine CT and lateral fluoroscopy in sleeping patients confirmed the CT results made in awake patients.\textsuperscript{42,44,45} In a rigorously controlled study conducted by Polo et al,\textsuperscript{46} patients with apnea, snoring nonapneic control subjects, and nonsnoring control subjects were studied when they were awake. Data were adjusted for differences in body size. Results showed narrowing of the retropalatal airway in the patients with apnea, different from nonsnoring control subjects, but not different from the snoring nonapneic subjects. In a study with ultrafast CT controlled for weight, but not age, Galvin et al\textsuperscript{47} demonstrated more inspiratory narrowing within both the oropharyngeal and retropalatal upper airway in patients with OSA than in control subjects. In this study, the snoring history of the control subjects was not documented. Thus, the results of CT examination show variable sites of upper airway obstruction in patients with OSA. Results in patients with OSA may not be different from those of nonapneic snorers. This latter finding needs confirmation.

Measuring pressure gradients across upper airway segments during sleep, three groups showed that inspiratory upper airway obstruction in patients with OSA occurred either in the retropalatal or the hypopharyngeal airway, duplicating the intersubject variability of the site of upper airway obstruction noted by CT scans.\textsuperscript{48-50}

Prediction of Surgical Success

The value of awake CT examination of the upper airway as a predictor of the success of UPPP has been studied. Gislason et al\textsuperscript{51} found the presence of wider tongues in poor responders to UPPP vs good responders. In a multiple regression analysis of body size, sleep apnea index, and radiographic variables to predict op-
operative success, the radiographic variables did not add significant predictability over clinical variables and the Müller maneuver in predicting the success of UPPP. In a retrospective study, Shepard and Thawley \cite{32} found that the whole upper airway cross-sectional area was not different between UPPP responders and nonresponders in their primary analysis. But, by comparing individual upper airway segment cross-sectional areas between responders and nonresponders, they found a better response to UPPP in those patients who had more narrowing in the retropalatal air space. Ryan et al \cite{53} showed that patients with the narrower oropharyngeal, not retropalatal, airway and those with a smaller upper airway volume did better following UPPP. These results suggest that CT analysis of the upper airway awake may not consistently be helpful in predicting the success of UPPP.

Using pharyngeal pressure measurements, Hudgel et al \cite{54} demonstrated that the success of UPPP was partially dependent on the location of the site of upper airway obstruction in that those with retropalatal obstruction had a borderline significantly better response to UPPP than those with retroglossal obstruction. Metes et al \cite{55} found that three of nine OSA patients with retropalatal obstruction and one of three with retroglossal obstruction, as determined by a pressure catheter, had a good response to UPPP. Three of the four responders to UPPP had retropalatal obstruction. Therefore, preoperative determination of the site of obstruction by intraluminal pressure gradient may be useful in defining those patients with retroglossal obstruction who will likely not respond favorably to UPPP. However, once identified, all these patients may not have a good response to UPPP.

Cephalometric analysis of the upper airway has been used to predict the success of pharyngeal surgery.\cite{56,57,58} Palate length, posterior airway space, mandibular position and plane, and hyoid bone position are variables identified to be abnormal in patients with OSA.\cite{56,57,58} This technique was more useful in demonstrating narrowing of the retroglossal airway than the retropalatal area. In nine OSA patients in whom UPPP failed, the posterior airway space was smaller and the hyoid bone position lower than in those who had a beneficial response to UPPP.\cite{59} These results suggest that the obstruction in UPPP failures involves the retroglossal airway.

The Müller maneuver has been used to assess upper airway collapsibility in OSA and to predict the results of upper airway surgery.\cite{60,61} Results have been mixed in that the maneuver is helpful in predicting the success of surgery in some instances and not in others. Sher et al \cite{60} performed UPPP on 30 OSA patients who had isolated retropalatal collapse as identified by the Müller maneuver during fiberoptic upper airway endoscopy. Surgical success was 73% (decrease in AHI of \( \geq 50\% \)). Patients with other sites of upper airway collapse noted with the Müller maneuver were not operated on, so essentially, this study is uncontrolled. However, the results are better than the usually accepted value of 50% response to UPPP. Katsantonis et al \cite{61} found the Müller maneuver to be helpful in predicting the success of UPPP in 12 of 24 OSA patients. In a study by Doghramji et al \cite{62} of 53 OSA patients who were screened to have retropalatal obstruction, neither the Müller maneuver nor cephalometrics was helpful in predicting the beneficial response to UPPP, which was only 32%, even in this preselected population. However, Aboussouan et al \cite{63} found that those OSA patients with retropalatal obstruction alone, as determined by the Müller maneuver, had a borderline significantly better response to UPPP than patients who also had a retroglossal component to their obstruction by this examination. The results of this latter study are somewhat difficult to interpret because several patients in the study had additional surgery, such as tonsillectomy or nasal surgery prior to their postoperative polysomnogram. These studies demonstrate that the Müller maneuver is not any better than other techniques in predicting a beneficial response to UPPP.

Direct visualization of the upper airway during sleep has also been used to predict the success of UPPP.\cite{64} In this study, a small-diameter nasoendoscope and pressure transducers were placed in the upper airway of OSA patients after local anesthesia. During sleep, during the first breath following the release of N-CPAP pressure, the change in airway cross-sectional area during inspiration could be measured at different sites within the upper airway. Results were interesting. There was poor agreement between sites of obstruction identified by an awake CT scan of the upper airway and those found by direct visualization during sleep. The authors categorized patients into those who had obstruction only within the nasopharynx (retropalatal airway) and those who had additional or isolated, more caudal sites of obstruction. The nasopharyngeal obstruction group had significantly better improvement than the group with more caudal obstruction at 4 months but not at 14 months following UPPP. At 4 months, 6 of 7 patients with isolated retropalatal obstruction had improved conditions, but only 2 of 11 patients with obstruction at other pharyngeal sites had improved conditions. Interestingly, only 2 of 7 with retropalatal obstruction continued to show improvement at 14 months postoperatively. Thus, direct visualization of the upper airway in sleep may identify patients who will have an initial favorable response to UPPP. How to maintain that improvement...
raises other issues, like maintenance of weight, changes in airway size, etc (see below).

MRI has been used to evaluate the upper airway in patients with OSA. Ultrafast MRI machines can be used to obtain images of upper airway anatomy during defined portions of the respiratory cycle. In ten patients with OSA, Shellcock et al.\(^6\) found isolated retropalatal obstruction or narrowing in four patients, isolated hypopharyngeal or oropharyngeal obstruction in four patients, and multiple sites of obstruction in two patients. To date and to our knowledge, this technique has not been used to predict the success of pharyngeal surgery.

**TYPE OF SURGICAL PROCEDURES USED**

The original surgery performed for OSA was the tracheostomy. Although tracheostomy was shown to be effective in decreasing the mortality and morbidity of OSA in one patient cohort,\(^56,67\) tracheostomies are often complicated by local infection and/or bleeding around the tracheostomy stoma. Aesthetically, tracheostomies are less than optimal from the patient’s perspective. Thus, it is not difficult to understand why otolaryngologists developed other operative procedures for the treatment of OSA. The most widely used technique is the UPPP. In general, this procedure is effective in one half the patients.\(^52,62,66,69\) Interestingly, UPPP seems to improve symptoms of OSA, even though minimal improvement is observed in the apnea pattern.\(^70\) The etiology of this seemingly paradoxical situation is unclear. UPPP does have an effect on upper airway physiology in that it decreases the collapsibility of the upper airway, although the success of surgery was not found to be predictable from the preoperative measurement of upper airway collapsibility.\(^71\)

The results of He et al.\(^4\) are somewhat alarming in that UPPP survival was no better than patients treated with dietary counseling. Larsson et al.\(^72\) reported their experience with a 4-year follow-up on 50 OSA patients treated with UPPP. Initially, 30 of 50 were classified as responders. After nearly 2 years, the number of responders was decreased to 19. These results are similar to those of Launois et al.\(^64\) noted above, demonstrating that the beneficial effect of UPPP may not be long lasting. Most of those failures over this time interval were in patients who had gained significant weight. These data indicate the need to do postoperative polysomnograms to detect initial nonresponders and to monitor patients long term to help them lose, or at least not gain, weight. If weight gain occurs post-UPPP, a polysomnogram may be advisable to detect worsening. If the apnea has reappeared or is worse, then N-CPAP may be needed. Of course, if weight gain has occurred, then dietary counseling should be reinstituted.

Other operative procedures have been used to treat OSA. To increase the caliber of the hypopharyngeal airway, the hyoid suspension and genioglossus advancement procedures were developed.\(^73-75\) It is difficult to examine the response to individual operative interventions, since they are often done in combination with other procedures. Johnson and Chinn\(^75\) reported a reduction of the AHI of at least 50% in six of nine patients studied with genioglossus advancement in addition to UPPP.

Another operative procedure that increases the hypopharyngeal cross-sectional area is mandibular advancement, done with or without maxillary advancement. Success has been variable, but generally better than that experienced with UPPP.\(^76-78\) Twenty of 21 patients with mandibular-maxillary deficiency and OSA had improved conditions with an average mandibular/maxillary advancement of 10 mm.\(^77\) In a study of patients referred for mandibular advancement for retroglossinathia, not OSA, Yu et al.\(^79\) found no relationship between the amount of mandibular, and/or mandibular/maxillary advancement, and change in the cross-sectional hypopharyngeal area, as measured by lateral cephalometric examination. Most interesting, these investigators found that the postoperative hypopharyngeal airway cross-sectional areas decreased over a mean follow-up period of 15 months. If there is a return toward the original airway size over time, then the long-term results with this procedure for OSA also may not be favorable, similar to new findings with UPPP.

Midline glossectomy has been proposed as simpler treatment of hypopharyngeal obstruction.\(^80\) Used in those who had not responded to UPPP, as well as in those patients who had not had a UPPP, but who demonstrated narrowing of the airway at the base of the tongue, midline glossectomy decreased the AHI to fewer than 20 events per hour of sleep in 17 of 22 OSA patients.\(^81\) Long-term follow-up is not available for this group of patients.

Riley et al.\(^82,83\) have taken a progressive approach to the surgical treatment of OSA. Surgery was planned for those who could not accept or tolerate N-CPAP. A preoperative examination of the upper airway was done with cephalometrics and the Müller maneuver. The operative approach depended on the identification of the site of obstruction or upper airway narrowing during these studies. Stage 1 surgery was the following: for those with retropalatal obstruction alone, a UPPP was performed; for patients with hypopharyngeal obstruction alone, genioglossus advancement and hyoid suspension were performed without UPPP; and for patients with obstruction at both sites, all three procedures were performed. Of the 239 patients who
entered this protocol, exclusive of those with severe OSA or severe mandibular deformities, most had the combined UPPP, genioglossus advancement and hyoid suspension. Of these, 61 percent were helped. (Gauges of improvement were as follows: an improvement in the AHI to under 20 events per hour, a reduction in the AHI of at least 50%, or subjective improvement which was as good as that experienced with N-CPAP.) For those who failed stage 1 surgery, stage 2 surgery was offered. This consisted of mandibular advancement. Twenty-four of 91 stage 1 failures accepted stage 2 surgery. Unfortunately, this group was combined with 60 UPPP-failure patients who were not originally in the protocol. The success rate of the stage 2 surgery was reported as 97%. Results were reported to not differ from those obtained in a N-CPAP-treated group, although it is not clear whether the surgical and N-CPAP groups were matched for gender, age, body mass index, and/or severity of OSA. Thus, a staged approach to the surgical treatment of OSA appears to be successful. If a preoperative analysis of the upper airway supine during sleep could be combined with a controlled study design for surgical treatment of OSA, more definitive results might be obtained. Such a study might be conducted in a group of OSA patients who are N-CPAP nonreceptors or N-CPAP failures, or who initially elect surgery. The following protocol could be followed: (1) preoperative upper airway obstruction site determination with either one or preferably a combination of Müller maneuver, cephalometrics, upper airway pressure measurements, and/or direct visualization during sleep; (2) UPPP on all; (3) if UPPP failure, perform midline glossectomy or genioglossus advancement/hyoid suspension; and (4) if this surgery fails, do a mandibular/maxillary advancement. Follow-up polysomnograms should be done at 3 to 6 and 12 to 18 months postoperatively. Retrospectively, preoperative obstructive site location would be examined to determine if the surgical results were predictable from the diagnostic studies. This analysis would be objective in establishing proper diagnostic tests to predict the results of surgery, as well as determine which form of surgery was best for which patients. Sequential studies would be designed to examine the results of the specific operative procedures, performed as a result of the diagnostic procedures.

Laser-assisted uvulopalatoplasty has been developed to treat snoring and OSA on an outpatient basis. However, little objective data are available to assess this procedure’s efficacy. After four to five sessions, in which the size of the uvula is reduced and the palate is scarred and made to retract due to vertical, linear "trenches" made at the base of the uvula, the apnea count, oxygenation, sleep efficiency, and snoring intensity all were shown to improve in 40 of 46 and 16 of 33 OSA patients. One drawback is that the conditions of some patients worsened with this procedure. Obviously, further study of this procedure is needed before it can be recommended for treatment of OSA.

Recent reports demonstrating a good response to dental appliances have appeared. These devices advance the mandible nonsurgically. Snoring, apnea counts, oxygenation, and sleep quality all improve with the dental appliance. Good compliance is reported, but of course, cannot be objectively assessed. Surely, these devices are a real therapeutic option. Problems are that there is no one best design, and dental laboratory assistance is required. More use of the dental appliance will clarify its role in the treatment of OSA.

**Pharmacologic Treatment of OSA**

Various pharmacologic agents have been used to treat OSA. None used to date has been completely successful, but some compounds are as effective as surgery, or maybe as effective as N-CPAP, if one uses the N-CPAP compliance data as a gauge of effectiveness of this therapy. If a truly effective and safe pharmacologic agent could be identified, such a treatment would be a convenient alternative to surgery or N-CPAP. Although, at this time such a pharmacologic panacea does not exist, there are some medications that show promise in treating at least a portion of OSA patients. How to identify patients who might respond to these medications and the identification of other agents that might be effective will be major challenges for the future.

There are several mechanisms by which pharmacologic agents might improve OSA, ranging from effects on sleep character to effects on neural control of breathing. For instance, some pharmacologic agents may alter sleep stage distribution and thereby decrease the time of the stage of sleep where the apneas predominate. Antidepressant agents decrease or nearly eliminate rapid eye movement (REM) sleep. If a given patient has most apneas in REM sleep, then a trial of a nonsedating antidepressant to diminish REM sleep time may be helpful. In contrast, if low ventilatory drive activity is present, as indicated by alveolar hypventilation awake, for instance as often occurs in hypothyroidism, then agents that stimulate ventilatory drive, such as thyroxine or medroxyprogesterone may improve the OSA in such a patient. Since OSA is more prominent in postmenopausal women, progesterone treatment may be especially helpful to the postmenopausal woman with OSA. Agents that eliminate periodic breathing in sleep, such as acetazolamide, may eliminate OSA in patients with an underlying dysrhythmia of ventilation. Pharmacologic agents that help
obese OSA patients lose weight should be helpful in the management of the OSA. Decongestant medications may decrease not only nasal congestion that may play a role in snoring in those with allergic or nonallergic rhinitis, but they may also decrease pharyngeal edema that is present in patients with OSA. In the following, a review of the use of specific agents will be provided.

Hypothyroidism and Acromegaly

Hypothyroidism and acromegaly are two endocrine abnormalities that are associated with OSA in adults. Surely, the possibility of hypothyroidism needs to be eliminated in the evaluation of the obese patients suspected of having OSA. If present, treatment of hypothyroidism with thyroxine replacement may resolve the OSA, even in hypothyroidism with obesity. It has been assumed that the cause of OSA in patients with hypothyroidism was the anatomic changes within the upper airway that occur as part of myxedema. However, treatment of the OSA in hypothyroid patients with medroxyprogesterone has been shown to be helpful. Suppressed ventilatory drive as well as the associated tendency for periodic breathing exist in hypothyroidism, and these factors may be important in producing OSA in patients with hypothyroidism. Treatment of acromegaly with a somatostatin analogue and bromocriptine has been shown to reverse the upper airway anatomic abnormalities and, subsequently, the OSA. Thus, these pharmacologic treatments may alleviate the need to bypass the upper airway with tracheostomy or use N-CPAP in acromegalic patients.

Acetazolamide

Agents such as acetazolamide enhance ventilatory drive and stability by producing a metabolic acidosis through inhibition of renal tubular secretion of hydrogen ion and by producing cerebral vascular dilation. Thereby, acetazolamide stimulates central ventilatory control and subsequently improves periodic breathing and OSA. Tijima et al showed moderate improvement in OSA with 250 mg of acetazolamide per day, a small dose but enough to change arterial blood gas status. Studying a small group of apnea patients with varied apnea patterns among them, Sharp et al demonstrated that acetazolamide was not very helpful in patients with primarily obstructive or central apnea. However, these investigators found that acetazolamide was somewhat useful in mixed apnea, where both a central and obstructive component exist within one apnea. In this study, obstructive apneas were produced during the acetazolamide treatment period in two of four patients who originally had mixed apneas (central apnea followed by an obstructive component). Shore and Millman found worsening of obstructive apnea with acetazolamide. The mechanism of this worsening is not known, although it is speculated that the metabolic acidosis preferentially stimulates the chest wall ventilatory pump muscles, and thereby increases the collapsing force applied to the upper airway by the chest wall inspiratory muscles in some individuals. The most significant adverse reaction to acetazolamide is paresthesia, which limits the dose tolerated. Thus, the therapeutic benefit of acetazolamide in patients with OSA has not been completely resolved. It appears that this agent may be good for some individuals, those primarily with periodic breathing or central apnea, and detrimental to others, possibly those with primarily obstructive apneas. Thus, a trial of 250 to 500 mg/d may be useful in patients with primarily Cheyne-Stokes breathing or central apnea. Close follow-up and a repeated polysomnography would be indicated a few days to weeks after initiation of treatment to verify a beneficial response.

Medroxyprogesterone

Medroxyprogesterone has been useful in some patients with sleep-disordered breathing. In healthy men, medroxyprogesterone, 60 mg/d, induced hyperventilation and brain and peripheral alkalosis, as well as greater exercise hyperpnea within 48 h of initiation of treatment. Interestingly, testosterone made OSA worse in some hypogonadal men. These studies illustrate a role for sex hormones in ventilation during sleep. In another study, four of nine (eight male and one female) OSA patients had improved conditions with 60 to 120 mg/d of medroxyprogesterone. Those whose conditions improved had more of an obesity-hypventilation component and had daytime hypoxemia and hypercapnia, indicative of alveolar hypoventilation. In a group of 21 postmenopausal women not specifically selected for ventilatory abnormalities, medroxyprogesterone decreased apnea duration, but it did not improve other apnea variables or oxygenation. In a group of 13 male OSA patients, Rajagopal et al found no improvement with medroxyprogesterone treatment even though resting ventilation and hypercapnic ventilatory drive were increased in these individuals during wakefulness. Menopausal replacement doses of estrogen and progesterone were not found to be effective. In addition, the feminizing effects of impotence at the high dose required for any ventilatory stimulation induced by medroxyprogesterone are problems often seen with its use in men. These studies with conflicting results make it difficult to recommend medroxyprogesterone use in patients with OSA. However, the obese female OSA patient with alveolar-hypoventilation may be an appropriate candidate for a therapeutic trial.
Theophylline

The ventilatory stimulant theophylline has been used sparingly in adults with OSA. Central, but not obstructive apneas were improved with an aminophylline IV infusion in 10 male OSA patients, but sleep quality was worsened by this treatment, even in the presence of a low therapeutic theophylline blood level.104 Guilleminault and Hayes105 found that neither short- nor long-term treatment with theophylline improved OSA. Mulloy and McNicholas106 found a decrease in apnea but a worsening of sleep quality in a placebo-controlled, crossover study. Therefore, theophylline appears to be of little use in adult OSA patients.

Opioid Antagonists

Increased cerebrospinal fluid opioid activity has been identified in patients with OSA.107 Therefore, it is logical to hypothesize that central stimulants or opioid antagonists would be helpful in OSA. Doxapram stimulates the CNS and carotid body chemoreceptors. Doxapram was found to decrease the length of apneas, but it did not alter the nocturnal average arterial oxygen saturation in four male OSA patients during an IV infusion.107 Although known to stimulate ventilation, naloxone was minimally helpful in OSA. Oxygenation, but not apnea frequency, was the only variable that improved, and only in one of the two studies reviewed.108,109

Nicotine

Nicotine stimulates upper airway muscles110 and thereby decreases upper airway resistance111 in animals. In eight male OSA patients, 14 mg of nicotine gum given over several hours prior to sleep onset significantly decreased the number of obstructive apneas and the total apneic time in the first 2 h of sleep without changes in sleep structure.112 In 20 nonsmoking OSA patients, transdermal nicotine did not improve apnea and worsened sleep quality in a well-controlled study.113

Angiotensin-Converting Enzyme Inhibitors

One group in Germany has reported beneficial effects of angiotensin-converting enzyme inhibitors in hypertensive OSA patients examined in unblinded studies.114,115 These studies primarily evaluated the antihypertensive effects of cilazapril during sleep. The authors provided very little detail about the effects of these medications on ventilation and OSA, except to comment that the apnea index decreased along with an improvement in nocturnal BP. Since the variability in BP and heart rate was reduced in patients studied by treatment of the hypertension, it was hypothesized that the sympathetic tone was reduced. It was proposed that this reduction in sympathetic tone would also decrease the variability in breathing and thereby improve the OSA. Because β-adrenergic-blocking agents reduce cardiac output and thereby possibly contribute to an increase in ventilatory variability and the tendency to develop periodic breathing and apneas, beta-blockers are not usually given to patients with OSA.

Psychotropic Agents

Various classes of psychotropic drugs have been used to treat OSA with a mixed degree of success. Antidepressant agents have been used to treat OSA. By decreasing the amount of REM sleep, the sleep state in which apneas are usually more severe than in other sleep stages, antidepressant agents improve OSA indirectly. In addition, these agents may work by stimulating upper airway motoneurons.116 Their primary pharmacologic effect is to prevent the reuptake of biogenic amines such as norepinephrine, dopamine, and serotonin at nerve terminals. This inhibition of reuptake increases the action of these amines, all known to be ventilatory drive and respiratory muscle stimulants.

Protriptyline, a dibenzocycloheptadiene, has been commonly used in OSA because it is nonseating.117-120 In an open-label study, Clark et al117 observed improvement in 8 of 14 OSA patients with an initial average apnea index of 60 events per hour. Responders took the medication for 7 to 15 months at a dose of 10 to 20 mg/d. In a placebo-controlled double-blind crossover of five male OSA patients, Brownell et al118 showed improvement in REM sleep stage apnea activity, daytime sleepiness, and nocturnal oxygenation. Conway et al119 demonstrated a better improvement in OSA patients with a baseline apnea frequency of fewer than 30 events per hour of sleep than in those with more severe disease. Smith et al120 found a significant decrease in apnea time, an improvement in oxygenation, and less daytime sleepiness with protriptyline. These investigators did not observe a relationship between the severity of OSA and the response to protriptyline. Whyte et al121 did not find any improvement with protriptyline treatment in a study of ten OSA patients. However, these investigators designed their study with 2-week trial periods of a placebo and another therapeutic agent, acetazolamide, in addition to protriptyline. There were no washout periods between therapeutic trials. In this study, protriptyline did not decrease the amount of REM sleep time. Therefore, it could be argued that the treatment period was not long enough to anticipate a pharmacologic effect of protriptyline or that there was not adequate workout time between trials. When used at a dose of 10 to 20 mg/d, protriptyline’s antimuscarinic effects were so strong that many people had
Initial Therapy

<table>
<thead>
<tr>
<th>Weight loss</th>
<th>Plus</th>
<th>Medications</th>
<th>or</th>
<th>nCPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>- for overnight OSA patients</td>
<td>Chosen to best fit the patient’s clinical and laboratory findings</td>
<td>6-8 weeks polysomnogram</td>
<td>Improved</td>
<td>Not Improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Medicine tolerated</td>
<td>nCPAP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continue</td>
<td>nCPAP</td>
</tr>
</tbody>
</table>

Tolerate | Not Tolerate

Continue | Medication or Surgery

6-8 weeks | 6-8 weeks polysomnogram

Improved | Not Tolerated | Improved | Not Improved

Continue | Surgery | Follow & | nCPAP or Further |

watch diet | Surgery |

FIGURE 1. Treatment algorithm for OSA.

trouble tolerating the medication. Men frequently experienced urinary hesitancy and/or frequency. Impotence was a common side effect. Therefore, protriptyline is a less than desired pharmacologic agent for the treatment of OSA in men.

Because serotonin is a sleep-inducing agent, and since it may be a ventilatory stimulant, tryptophan and serotonin reuptake blockers have been used to treat OSA. In an uncontrolled study, L-tryptophan taken for a variable period, from days to weeks, significantly decreased apnea index in a group of 12 OSA patients. From this study, it might be concluded that enhancement of serotoninergic activity may improve OSA. However, because eosinophilia-myalgia syndrome and pulmonary disease have been reported with L-tryptophan ingestion, L-tryptophan is no longer available on the US market. In an open-label comparison with protriptyline, Hanzel et al found that fluoxetine improved the AHI or the oxygen saturation index (number of desaturation events per hour of sleep) by 50% or greater in 5 of 12 patients and improved the AHI significantly in the whole group. With protriptyline, the OSA worsened in one patient. Three of the 12 patients were unable to complete the protriptyline trial because of the adverse effects mentioned above, even at 10 mg/d, but they could tolerate fluoxetine. Fluoxetine produces mild anorexia and occasional G1 side effects. Wild ideations, a focus of much of the lay press on fluoxetine, are rare. Further work will be needed to determine whether serotoninergic agents are truly useful in OSA.

Buspirone, a serotonin agonist and a nonsedating asapione anxiolytic agent that stimulates ventilation in animals and stimulates ventilatory drive in humans, was shown to decrease the number of apnea events by one third in a group of five sleep apnea patients in a double-blind, random-sequence design. Unfortunately, apneas actually worsened in one patient. These preliminary, but promising results await confirmation by a larger study.

Benzodiazepines

Clonazepam, a benzodiazepine often used to treat periodic leg movement, was shown to decrease the number of obstructive apneas in two patients who had both OSA and periodic leg movement. It was hypothesized the clonazepam interrupted the cycle of leg movement-induced sleep fragmentation, which might induce an abnormal breathing pattern during sleep. The idea of inducing sleep continuity of sleep to resolve OSA has merit, but the use of benzodiazepines to accomplish this goal is potentially dangerous because of the ventilatory depressant action of these agents.
CONCLUSION

Much work remains ahead to identify effective pharmacologic agents for OSA. Once identified, these agents must be tested in representative patient groups with a double-blind, placebo-controlled study design in multicenter trials to test the value of these agents. Because of the poor patient compliance to N-CPAP and the less-than-ideal success of upper airway surgery, the continued search for more effective pharmacologic agents is surely worthwhile.

Therapeutic Approach to OSA

When presenting the therapeutic alternatives to a patient with OSA, the health-care provider should review the pros and cons of each of the categories discussed herein: (1) weight loss; (2) N-CPAP; (3) surgery; and (4) medications. Three primary principles are best followed: (1) honor the patient’s desires; (2) follow-up the results of therapy initiated; and (3) if one therapy is not effective or is dissatisfying to the patient, switch to another form of therapy. The following algorithm (Fig 1) is offered to guide therapy for the patient who does not have a sense of direction or seeks his/her physician’s advice. This algorithm is intended for the “average” patient with sleep apnea and does not apply to an extremely ill person or to a complicated case. Surgery may be considered earlier than presented in the algorithm if a local pharyngeal anatomic abnormality is obvious.

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