Practice Parameters for the Medical Therapy of Obstructive Sleep Apnea

Standards of Practice Committee of the American Academy of Sleep Medicine

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Summary: Therapies for obstructive sleep apnea other than positive airway pressure, oral appliances, and surgical modifications of the upper airway are reviewed in this practice parameter. Several of these therapies such as weight loss and positional therapy hold some promise. Others, such as serotonergic agents, may gain credibility in the future but lack well-designed clinical trials. No practice parameters could be developed for a number of possible therapeutic modalities that had little or no evidence-based data on which to form a conclusion. The role of an organized, targeted weight-loss program either as a single therapy or as a supplement to PAP needs to be clarified. Although bariatric surgery is increasingly performed for refractory medically complicated obesity, its long-term effectiveness in treatment of obstructive sleep apnea in morbidly obese patients is not yet demonstrated. Positional therapy, or methods for preventing sleep in the supine position, has probably been underutilized due to lack of easily measured predictive factors and randomized controlled trials.

Keywords: Obstructive sleep apnea, medical therapy, weight reduction, bariatric surgery, positional therapy, supplementary oxygen, selective serotonergic uptake inhibitors.

Citation: Morgenthaler TI; Kapen S; Lee-Chiong T et al. Practice parameters for the medical therapy of obstructive sleep apnea. *SLEEP* 2006;29(8):1031-1035.

1.0 INTRODUCTION

OBSTRUCTIVE SLEEP APNEA (OSA) IS A PREVALENT MAJOR HEALTH HAZARD WITH SERIOUS HEALTH CONSEQUENCES INCLUDING EXCESSIVE DAYTIME sleepiness (EDS), cognitive disturbances and depression, hypertension, and cardiovascular and cerebrovascular disease.[1-7] Since its introduction in 1981, positive airway pressure (PAP) has been the most efficacious therapy and is often the first option for OSA patients.[8] For patients with mild or moderate OSA, oral appliances may also be appropriate therapy.[9] However, some patients find such devices to be intrusive, inconvenient, or intolerable.[10] Surgical modification of the upper airway is also a viable treatment for selected patients.[11] Not all patients adapt or respond well to these options, and more treatment alternatives are desirable.

Obesity is one of the most important risk factors for OSA. Consequently, maintenance of ideal weight and weight loss might be important strategies for the management of OSA, either together with other therapies or as stand-alone treatments. Positional therapy is based on the tendency of OSA to worsen in the supine position. Recognizing that pharmacologic agents may influence sleep stage and have differential effects on respiratory muscle control, several medications have been tested in OSA patients with the goal of achieving a safe, effective, and noninvasive mode of therapy. Finally, oxygen administration has been tested as a means to alleviate the effects of OSA. Although lifestyle changes such as weight loss and positional therapy, surgically-aided weight loss, pharmacotherapy, and oxygen administration may also be viable treatment options, less attention has been paid to them in the literature.

The purpose of this practice parameter paper is to provide recommendations regarding the use of medical therapy (which we define as therapies other than modification of upper airway patency with devices or surgical interventions which are covered in previous practice parameters) for the treatment of OSA.[8,9,11] Recommendations are based on the accompanying review paper produced by a Task Force established by the Standards of Practice Committee.[12] Recommendations are targeted to the practice of adult sleep medicine.

Disclosure Statement

This was not an industry supported study. Dr. Morgenthaler has received research support from Itamar Medical Ltd. and ResMed Research Foundation; and has received research equipment from Olympus. Dr. Alessi is a consultant for Prescription Solutions, Inc. Dr. Coleman is a member of the Medical Advisory Board for Influent and is a consultant and speaker/instructor for Acclarent. Dr. Kapur has received research support from Pro-tech Services, Inc.; and has received research equipment from Respironics. Dr. Owens has received research support from Eli Lilly, Cephalon, and Sepracor; is a consultant for Eli Lilly, Cephalon, Shire, and Sanofi-Aventis; and has participated in speaking engagements supported by Eli Lilly, Cephalon, Sanofi-Aventis, and Johnson & Johnson. Dr. Swick has received research support from Sanofi-Aventis, Takeda Pharmaceuticals, Merck, Jazz Pharmaceuticals, Pfizer, Somaxon, Astellas-Pharmaceuticals, and Cephalon; and is on the speakers' bureau of GlaxoSmithKline, Jazz Pharmaceuticals, Sepracor, Cephalon, and Boehringer Ingelheim. Dr. Hirshkowitz has received research support from Sanofi-Aventis, Takeda, Merck, GlaxoSmithKline, Cephalon, Sepracor, Respironics, ResMed, and NBI; is on the speakers' bureau of Sanofi, Takeda, and Cephalon; is a consultant for Sanofi-Synthelabo, Takeda, and Cephalon; and has received research equipment from ResMed, Respironics, Sunrise, Puritan Bennett, Itamar, Nasal Aire, and Fisher-Paykel. Drs. Kapen, Lee-Chiong, Boehlecke, Brown, Friedman, and Pancer have indicated no financial conflicts of interest.

Submitted for publication March 9, 2006
Accepted for publication March 9, 2006

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2.0 METHODS

The Standards of Practice Committee of the AASM developed these practice parameters based on the accompanying review paper.[12] A Task Force of content experts was appointed by the AASM to review and grade evidence in the scientific literature regarding therapies for OSA not covered by previous practice parameters.

The Board of Directors of the AASM approved these recommendations. All members of the AASM Standards of Practice Committee and Board of Directors completed detailed conflict-of-interest statements and were found to have no conflicts of interest with regard to this subject.

These practice parameters define principles of practice that should meet the needs of most patients in most situations. These guidelines should not, however, be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding propriety of any specific care must be made by the physician, in light of the individual circumstances presented by the patient, available diagnostic tools, accessible treatment options, and resources.

The AASM expects these guidelines to have an impact on professional behavior, patient outcomes, and, possibly, health care costs. These practice parameters reflect the state of knowledge at the time of publication and will be reviewed, updated, and revised as new information becomes available. This parameter paper is referenced, where appropriate, using square-bracketed numbers to the relevant sections and tables in the accompanying review paper, or with additional references at the end of this paper. The Standards of Practice Committee's classification of evidence for evidentiary articles is listed in Table 1. Definitions of levels of recommendations used by the AASM appear in Table 2.

Table 1 – AASM Classification of Evidence

Evidence Levels	Study Design
I	Randomized well-designed trials with low alpha and beta levels *
II	Randomized trials with high alpha and beta levels*
III	Nonrandomized concurrently controlled studies
IV	Nonrandomized historically controlled studies
V	Case series

Adapted from Sackett, 1993[13]
*Alpha (type I error) refers to the probability that the null hypothesis is rejected when in fact it is true (generally acceptable at 5% or less, or $p<0.05$). Beta (Type II error) refers to the probability that the null hypothesis is mistakenly accepted when in fact it is false (generally trials accept a beta error of 0.20). The estimation of Type II error is generally the result of a power analysis. The power analysis takes into account the variability and the effect size to determine if sample size is adequate to find a difference in means when it is present (Power generally acceptable at 80-90%).

Table 2 – AASM Levels of Recommendations

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

Adapted from Eddy[14]

3.0 RECOMMENDATIONS

The following are recommendations of the Standards of Practice Committee and the Board of Directors of the American Academy of Sleep Medicine. The classification of evidence was adapted from the suggestions of Sackett (Table 1). Recommendations are given as standards, guidelines and options, as defined in Table 2.

3.1 WEIGHT REDUCTION

3.1.1 Successful dietary weight loss may improve the apnea-hypopnea index (AHI) in obese obstructive sleep apnea (OSA) patients [3.1]. (Guideline)

This parameter is based on one Level I, one Level II, and 2 Level III papers.[15-18] All papers reported an improvement in indices of OSA with successful weight loss. One Level I and one of the Level III papers relied on oxygen desaturation indices (ODI) instead of AHI. Kajaste et al followed their patients up to 24 months during which time there was a trend towards regaining weight along with a lesser degree of improvement of ODI.

3.1.2 Dietary weight loss should be combined with a primary treatment for OSA.[8,9,11] [3.1] (Option)

This recommendation is based on the same sources as in 3.1.1. While most studies indicate improvement in measures of OSA in patients with moderate to severe OSA, few were cured by dietary approach alone. There are little data regarding success of dietary management on mild OSA. Furthermore, PAP, dental devices, and surgery have an immediate effect whereas the response to diet is delayed. Therefore, while dietary weight loss is recommended as a component of therapy for obese patients with OSA, this approach should be combined with a proven treatment.

3.1.3 Bariatric surgery may be adjunctive in the treatment of OSA in obese patients. [3.1] (Option)

There are no Level I-III studies of bariatric surgery for OSA specifically.[19-21] However, many non-randomized, uncontrolled investigations are now available, show improvements in AHI with weight loss, and therefore there is consensus among members of the Task Force and the Standards of Practice Committee that bariatric surgery may play a role in the treatment of morbidly obese OSA patients as an adjunct to less invasive and rapidly active first-line therapies such as PAP.[22] A cautionary note is warranted because of reports of recurrence of OSA after several years even without regaining of weight.[23,24] Also, bariatric surgery is not without complications as is documented in several reviews published in 2004.[25]

3.2 PHARMACOLOGIC AGENTS

3.2.1 Selective serotonergic uptake inhibitors (SSRIs) are not recommended for treatment of OSA. [3.2.1] (Standard)

The above recommendation is derived from 2 Level II publications and one level V using paroxetine and fluoxetine.[26-28] The use of selective serotonergic uptake inhibitors (SSRI) has not led to consistent or significant improvement in the AHI of OSA patients and cannot be recommended for the treatment of OSA. As is stated in the accompanying review paper, there are multiple serotonergic receptors and different effects of serotonergic agents on central (brainstem) as opposed to peripheral (upper airway) receptor sites such that it is likely that only a targeted approach will lead to definitive conclusions on the efficacy of serotonergic agents in the treatment of OSA[3.2.1].

3.2.2 Protriptyline is not recommended as a primary treatment for OSA. [3.2.2] (Guideline)

Three Level II and one Level V papers form the basis of this recommendation.[29-32] One of the level II studies showed no improvement on either AHI or oxygenation parameters.[31] Although protriptyline may induce a moderate improvement in the AHI of OSA patients and may also partially prevent oxygen desaturation, many patients in the referenced studies had significant residual OSA. All of these papers were published in the 1980s and there have been no more recent evaluations of protriptyline for the treatment of OSA. The mechanism of protriptyline's favorable effects is via its suppression of REM sleep by virtue of its uptake inhibition of the monoamines, serotonin and noradrenalin. Another REM sleep suppressant medication, clonidine, showed mixed results for the treatment of OSA.

3.2.3 Methylxanthine derivatives (aminophylline and theophylline) are not recommended for treatment of OSA. [3.2.3] (Standard)

For this recommendation, there are 3 Level II publications, all of which report similar negative findings.[33-35] In these studies they had clinically insignificant effects on the AHI. The possible usefulness of these medications for the treatment of central sleep apnea is not covered by this recommendation.

3.2.4 Estrogen therapy (estrogen preparations with or without progesterone) is not indicated for the treatment of OSA. [3.2.4] (Standard)

This recommendation, which is based on the results of 4 Level I, 3 Level II, and one Level V publications.[36-43] Some papers reported negative results and others reported only minor improvements which are probably not clinically significant. Based on these results, neither primary estrogen replacement therapy nor supplementary therapy with estrogens, whether with estrogen alone or coupled with progesterone, is recommended for the purpose of treating obstructive sleep apnea. There are also potential adverse side-effects associated with the administration of estrogen replacement therapy.[44]

3.2.5 Modafinil is recommended for the treatment of residual excessive daytime sleepiness in OSA patients who have sleepiness despite effective PAP treatment and who are lacking any other identifiable cause for their sleepiness. [3.2.4] (Standard)

All five studies included in the review (3 Level I, one Level II, and one Level V) attest to the partial effectiveness of modafinil in the management of residual sleepiness in patients with treated OSA who have no other identifiable reason for hypersomnolence.[45-49] Blood pressure must be monitored because of mild elevations reported in some OSA patients using modafinil.[50] Before turning to modafinil, other causes of residual sleepiness must be ruled out including: non-compliance with PAP; ill-fitting PAP masks; insufficient sleep; poor sleep hygiene; other sleep disorders such as narcolepsy or restless legs syndrome/periodic leg movements of sleep; and depression.

3.3 SUPPLEMENTAL OXYGEN

3.3.1 Oxygen supplementation is not recommended as a primary treatment for OSA. [3.3] (Option)

There are 2 Level II and 2 Level III studies that show oxygen administration improves oxygenation parameters in patients with OSA.[51-54] Three of these studies involved special populations of OSA patients; one evaluated 3 patients on long term opioid therapy,[52] one studied 43 patients who had already undergone not fully successful surgical management of OSA,[53] and one involved 8 CPAP intolerant males.[54] The remaining study primarily reported on the effect of transtracheal oxygen therapy in 4 patients, 3 of whom had significant obstructive lung disease. Although all studies showed favorable effects on oxygenation, the effect of oxygen therapy on apneas, hypopneas and subjective sleepiness was inconsistent.

3.4 MEDICAL THERAPIES INTENDED TO IMPROVE NASAL PATENCY

3.4.1 Short-acting nasal decongestants are not recommended for treatment of OSA. [3.4] (Option)

One level II study showed little additive effect of oxymetazoline to positional therapy in improving AHI.[55] There are reasonable concerns that topical decongestants which work through mucosal vasoconstriction typically have rebound vasodilation that would adversely effect nasal patency over intervals typical of total sleep times. Chronic use leads to rhinitis medicamentosa in susceptible individuals.[56] Until there are more data available we recommend against the use of these agents as chronic therapy for nasal congestion in patients with OSA.

3.4.2 Topical nasal corticosteroids may improve the AHI in patients with OSA and concurrent rhinitis, and thus may be a useful adjunct to primary therapies for OSA. [3.4] (Guideline)

This recommendation is based upon the results of one level I study that demonstrated an improvement in mean AHI from 20 to 12 events/hr using fluticasone nasal spray.[57] Additionally, there is general support in the medical literature for treatment of nasal congestion with topical nasal corticosteroids.[58] Although this one study demonstrated improvement in mean AHI, individual responses may vary, and therapeutic response should be individually assessed.

3.5 POSITONAL THERAPIES

3.5.1 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. [3.5] (Guideline)

Patients who normalize their AHI when they sleep in a non-supine position tend to have less severe OSA, to be less obese, and to be younger. Three Level II studies form the basis for this practice parameter, one of which compared supine with an upright position.[59-61] Because not all patients normalize AHI when non-supine, the committee's opinion is that correction of OSA by position should be documented with an appropriate test.[62,63] In addition, 2 papers have described special pillows which improved OSA.[64,65]

4.0 OTHER MEDICAL THERAPIES

Listed here are medical therapies for which no or insufficient data were present in the literature to support the formulation of practice parameters. They include: nicotine; thyroid hormone for patients with hypothyroidism; bromocryptine for patients with acromegaly; androgen blockade; medroxyprogesterone for male OSA patients; and mirtazepine [3.2.1; 3.2.3; 3.2.4; 3.4].

5.0 RECOMMENDATIONS FOR FUTURE RESEARCH

1. The effects of dietary weight reduction need to be evaluated in large randomized, placebo controlled studies and predictive factors should be developed. Large prospective studies are needed for effects of bariatric surgery including treatment effects on sleep parameters such as continuity and architecture. Research should help clarify which types and severities of sleep-related breathing disorders respond to weight reduction, and focus on the long term neurophysiologic and cardiovascular outcomes. Collaboration between sleep medicine and weight reduction clinics would be most likely to produce useful data.
2. Standardized approaches for the maintenance of a non-supine position during sleep should be developed in clinical trials. These might include positional alarms, sleep shirts, and special pillows. The role of positional therapy, indicators for treatment response, and long term outcomes should be clarified in large-sample, well-designed studies.
3. In light of the successful treatment of unexplained residual sleepiness in PAP-treated OSA patients, the effects of methylphenidate should be investigated as a low-cost alternative to modafinil. Additionally, an investigation of the effects of long term use of stimulants in patients with residual hypersomnolence on physiologic (e.g. cardiovascular) and neurobehavioral outcomes is needed before these treatments become firmly entrenched as "usual treatment" of selected patients with OSA.
4. Further research on serotonergic agents is desirable in view of their important peripheral and central effects on upper airway mechanisms and the potential inherent in targeting specific receptor types. Experimental laboratory animal investigations would be best suited to differentiate central from peripheral effects.

ACKNOWLEDGMENTS

The AASM and the SPC would like to thank Sara Seaquist and Maria DeSena for coordinating the work on this practice parameter and to Richard Rosenberg, PhD, Andrew L. Chesson, MD, and Max Hirshkowitz, PhD for their contributions to the preparation of the manuscript.

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