Medical Therapy for Obstructive Sleep Apnea: A Review by the Medical Therapy for Obstructive Sleep Apnea Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine

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Abstract: A significant number of patients with obstructive sleep apnea neither tolerate positive airway pressure (PAP) therapy nor achieve successful outcomes from either upper airway surgeries or use of an oral appliance. The purpose of this paper, therefore, was to systematically evaluate available peer-reviewed data on the effectiveness of adjunctive medical therapies and summarize findings from these studies. A review from 1985 to 2005 of the English literature reveals several practical findings. Weight loss has additional health benefits and should be routinely recommended to most overweight patients. Presently, there are no widely effective pharmacotherapies for individuals with sleep apnea, with the important exceptions of individuals with hypothyroidism or with acromegaly. Treating the underlying medical condition can have pronounced effects on the apnea/hypopnea index. Stimulant therapy leads to a small but statistically significant improvement in objective sleepiness. Nonetheless, residual sleepiness remains a significant health concern. Supplemental oxygen and positional therapy may benefit subsets of patients, but whether these therapies reduce morbidities as PAP therapy does will require rigorous randomized trials. PAP therapy has set the bar high for successful treatment of sleep apnea and its associated morbidities. Nonetheless, we should strive towards the development of universally effective pharmacotherapies for sleep apnea. To accomplish this, we require a greater knowledge of the neurochemical mechanisms underlying sleep apnea, and we must use this infrastructure of knowledge to design well-controlled, adequately powered studies that examine, not only effects on the apnea/hypopnea index, but also the effects of pharmacotherapies on all health related outcomes shown beneficial with PAP therapy.

Keywords: Sleep apnea, obesity, weight loss, low calorie, bariatric, pharmacotherapy, serotonergics, protriptylline, modafinil, supplemental oxygen, position, cervical pillow

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1.0 INTRODUCTION

OBSTRUCTIVE SLEEP APNEA (OSA) IS A HIGHLY PREVALENT SYNDROME THAT IS ASSOCIATED WITH SUBSTANTIAL MORBIDITY AND INCREASED MORTALITY.[1-10] Positive airway pressure (PAP) is the most uniformly effective therapy, and to date this is the only intervention for OSA shown to have a favorable impact on both cardiovascular and neurobehavioral morbidities.[1,2,6] However, approximately 25-50% of patients with OSA will either refuse the offer of PAP therapy, or will not tolerate it.[11] Oral appliances and surgical procedures to improve upper airway patency are successful in certain subsets of patients, but a notable proportion of patients do not receive adequate clinical benefit from these approaches. In addition, many individuals treated with PAP therapy experience residual sleepiness, despite marked improvements in the apnea-hypopnea index.[12,13] Therefore, medical therapies may be considered for the subsets of patients who will not or cannot use PAP and for patients with residual sleepiness despite alleviation of upper airway obstruction during sleep by mechanical devices such as PAP or oral appliances, or upper airway surgery.

The charge given to this task force was to review literature on clinical trials regarding alternative and/or adjunctive medical therapies, such as weight reduction, pharmacotherapies (e.g., targeting the pathophysiology underlying the OSA, the sleepiness or nasal obstruction), delivery of supplemental oxygen and positional therapies. To aid in patient management, we have provided an overview of the effectiveness of various medical therapies, by describing the study designs, findings and limitations of each category of medical therapy. It is hoped that this review will provide a basis for improving the design of future studies, as we continue to search for more effective medical therapeutic options for patients with obstructive sleep apnea. Concerning terminology, although studies inconsistently defined obstructive sleep apnea-hypopnea syndrome (OSA), in the spirit of simplicity, we will only use the term OSA and report the apnea-hypopnea index (AHI) or apnea index in reviewing individual papers.

2.0 METHODOLOGY

A PubMed search (http://www.ncbi.nlm.nih.gov/entrez/query.

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fcgi) was conducted for key words: sleep apnea or obstructive sleep apnea with bariatric surgery, diet, therapy, oxygen, supplemental oxygen, drug therapy, pharmacotherapy, medical, endocrine, position, weight reduction, weight loss, rhinitis, nasal symptoms, nasal therapy. Literature searches were limited to clinical studies published in the English language between 1985 and January 2005. A search update in April 2005 was conducted on PubMed for "obstructive sleep apnea" and "therapy" with screening of abstracts to ensure completeness of review. Inclusion criteria for the articles included: English language, clinical trials, polysomnography end-points of apnea and/or hypopnea indices and adult subjects. Exclusion criteria included case reports, subjects <20 years of age and use of non-FDA-approved medications. Studies described in this report have each been characterized with evidence levels using criteria listed in Table 2. In addition to reviewing pertinent findings in the studies meeting the inclusion/exclusion criteria, we present data from additional studies, where further insight has been gained.

3.0 RESULTS

Of the 1750 abstracts identified by the key word search, 135 studies were identified as qualifying for the above inclusion and exclusion criteria and relevant to the categories of weight loss, pharmacotherapies, delivery of supplemental oxygen and positional therapy. Overall, most of the qualifying studies identified provided Level II or Level III evidence for the effectiveness of an intervention on improving the AHI (Refer to Table 1 for evidence level definitions). Very few studies presented data on neurobehavioral, metabolic or cardiovascular outcomes. In addition, very few of the papers compare medical therapies to CPAP outcomes.

1.1 Weight Reduction

The effectiveness of weight loss in treating OSA was examined. All methods for achieving the weight reduction were considered for this review. Consequently, studies that described either medical (e.g. dietary modification) or surgical weight loss were evaluated. A total of 39 papers qualified for review. The majority of weight loss and sleep apnea studies identified by the search were case series evaluating the effects of bariatric surgery upon weight and concurrent obstructive sleep apnea in severely obese patients, as detailed below. The remainder of studies evaluated the effects of low calorie and very low calorie dietary programs to achieve weight reduction in more moderately overweight patients, both in hospital and home environments. Overall, weight reduction was associated with reductions in the AHI for both surgical and reduced calorie therapies. The magnitude of weight reduction achieved by bariatric surgery generally far exceeded that reported after medical intervention. Adverse outcomes in both medical and surgical studies were incompletely described. Most identified studies that reported weight loss effects on OSA lacked control groups, randomized design, or sufficiently high alpha and beta error to provide strong support for clinical practice guidelines. Moreover, few studies have examined the long-term effects of weight loss therapies on OSA.

Of three dietary therapy studies with higher evidence scores (Level II or III), two were non-randomized controlled trials examining the effects of weight loss on the AHI. In the study by Rauscher and colleagues,[14] 60 patients were encouraged to lose weight, with 33 of these accepting the regular use of nasal continuous positive airway pressure (CPAP) and 27 receiving no additional therapy. Subjects treated with CPAP realized a small reduction in body mass index (BMI, weight (kg)/height, (m^2) from 32.3 + 1.2 kg/cm^2 to 31.7 + 1.3 kg/cm^2, $p < 0.05$, while the group treated with weight loss alone showed no significant change. Subjects in this study self-selected CPAP, and therefore, the effects of CPAP use on weight loss cannot be determined. The effect of weight loss on AHI without CPAP was not reported. As a result, this study was insufficient to support a clinical guideline for weight loss advice.

Schwartz and colleagues[15] (level III) reported a non-randomized controlled trial of 26 male subjects with OSA (AHI > 10), 13 of whom were treated with a low calorie diet plan for weight reduction, and 13 of whom received standard care (control group). The subjects who were offered dietary modification demonstrated a significant reduction in weight (BMI decreased from 42 ±7 to 35 ±5, SE, p=0.0.001), critical closing pressure for the upper airway fell from 3 cm H_2O to -4 cm H_2O (indicating a much less collapsible airway), and the AHI fell significantly from 83 to 33 events per hour, p<0.0001. The control group demonstrated no change in weight, upper airway collapsibility or AHI.

Smith and associates[16] (level II) studied 23 obese patients with OSA randomized to either usual care (n=8) or weight reduction via a low calorie diet (n=15). Approximately 5 months into the protocol, the weight reduction group had lost an average 0.45 kg per week. Weight reduction was associated with reductions in AHI from 55 to 29 events per hour during non-REM sleep, and from 57 to 38 events per hour during REM sleep. The 8 control patients did not lose weight and demonstrated no change in AHI. This non-randomized controlled trial was assigned as level II evidence.

Two Finnish studies used oxyhemoglobin desaturation index, rather than a polysomnographically-defined AHI, as the primary endpoint.[17,18] The two studies are reviewed primarily because of the long-term follow-up that was reported. Kajaste et al. performed a randomized control trial testing the effectiveness of a cognitive behavioral weight reduction program. Obese middle-age males (n=31) lost an average weight > 20 kg in the first year. Although there was some weight gain in the second year, subjects on average were 25 kg below the starting weight. At the two year

Table 1 – *AASM Classification of Evidence

Evidence Levels	Study Design
I	Randomized well-designed trials with low-alpha & low-beta errors*
II	Randomized trials with high-beta errors*
III	Nonrandomized controlled or concurrent cohort studies
IV	Nonrandomized historical cohort studies
V	Case series

Adapted from Sackett, 1993

*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 –Table of Studies and Their Evidence Level Assignments (For more detailed and extensive data table, see online supplement @ www.sleepnet.waytoodetailedformost .

Author	Year	Subject	Evidence Level
Non-Drug Studies			
Cartwright et al	1985	Positional Therapy	III
Cartwright et al	1991	Positional and Nasal Therapy	II
Fisher	2002	Weight Loss - Low Calorie Diet	IV
Guardiano et al	2003	Weight Loss - Bariatric	IV
Jokic et al	1999	Positional vs. CPAP	II
Kansanen et al	1998	Weight Loss - Low Calorie Diet	V
Schonhofer & Kohler	1996	Weight Loss - Bariatric	I
Kushida et al	2001	Non-serotonergic REM sleep Suppressant Therapy	III
Kushida et al	1999	Positional Therapy	III
Lojander et al	1998	Weight Loss - Low Calorie Diet	III
Mcevoy et al	1986	Positional Therapy	III
Miki et al	1988	Positional Therapy	III
Nahmias et al	1993	Weight Loss vs. CPAP	III
Neill et al	1999	Positional Therapy	III
Noseda et al	1996	Weight Loss vs. CPAP	III
Peppard et al	2000	Weight Loss - Low Calorie Diet	III
Perl-Aljadeff et al	1996	Supplemental Oxygen	III
Perl-Chauncey	1990	Oxygen therapy - Transtracheal	II
Perl-Farney et al	1992	Oxygen Therapy	II
Perl-Landsberg et al	2001	Supplemental Oxygen	III
Perl-Marcus et al	1995	Supplemental Oxygen	III
Perl-Phillips et al	1990	Supplemental Oxygen	II
Perl-Rajagopal et al	1984	Ventilatory Stimulant- Doxapram	II
Perl-Smith et al	1984	Weight Loss - Low Calorie Diet	II
Sampol et al	1998	Weight Loss - Low Calorie Diet	V
Schwartz et al	1991	Weight Loss - Bariatric and Low Calorie	III
Series & Marc	2001	Positional vs. CPAP	II
Smith et al	1985	Weight Loss - Low Calorie Diet	II
Drug Studies			
Berry et al	1999	Serotonergic Therapies	II
Braver & Block	1994	Postural Therapy and Nasal Therapy	II
Braver et al	1995	Weight Loss + Nasal Spray Therapy	V
Finnimore	1995	Baclofen Therapy	I
Hedner et al	2003	Perl	I
Hoijer et al	1992	Benzodiazepine Therapy	I
Kraiczi et al	1999	Paroxetine Therapy	II
Perl- Mulloy & McNicholas	1992	Aminophylline Derivatives	II
Perl-Arnulf et al	1997	Modafinil Therapy	I
Perl-Atkinson et al	1985	Naloxone Therapy	III
Perl-Black et al	2004	Modafinil Therapy	I
Perl-Brouillette	2001	Nasal Therapy	II
Perl-Cook	1989	Hormonal Therapy-Males	III
Perl-Davila et al	1994	Nicotine Patch Therapy	I
Perl-Espinoza et al	1987	Aminophylline Derivatives	III
Perl-Grunstein et al	1994	Medical Illness Targeted Therapy	III
Perl-Hein et al	2000	Aminophylline Derivatives	II
Perl-Heissman J et al	1999	Modafinil Therapy	II
Perl-Issa	1992	Clonidine Therapy	III
Perl-Kiely et al	2004	Nasal Therapy	I
Perl-Kingshott	2001	Modafinil + CPAP Therapy	II
Perl-Liu et al	2003	Hormonal Therapy-Males	II
Perl-Manber, et al	2003	Hormonal Therapy - Female	II
Perl-Polo-Kantola et al	2003	Hormonal Therapy - Female	II
Perl-Rajagopal et al	1986	Hormonal Therapy - Female	III
Perl-Saletu et al	1999	Aminophylline Derivatives	II
Perl-Shahar et al	2003	Hormonal Therapy - Female	III
Perl-Stepanski et al	1988	Non-serotonergic REM sleep Suppressant Therapy	II
Perl-Stewart	1992	Hormonal Therapy-Males	III
Perl-Stradling et al	2003	Serotonergic Therapies	II
Perl-Strohl et al	1981	Medroxyprogesterone	II
Perl-Whyte et al	1988	Non-serotonergic REM sleep Suppressant Therapy	II
Perl-Zevin et al	2003	Ventilatory Stimulant - Nicotine	II
Perl-Ziemer et al	1988	Hormonal Therapy - Females and Males	III
Suratt et al	1986	Ventilatory Stimulant - Doxapram	II

point, the oxyhemoglobin desaturation index (≥4% desaturations) fell by 50% in 40% of the subjects studied. Changes in weight correlated strongly with changes in the oxyhemoglobin desaturation index.[18] In the earlier study using a very low calorie diet a similar weight loss was observed as well as a similar effect on the frequency of nocturnal oxyhemoglobin desaturations.[17] This study also reported large improvements in both blood pressure and baroreceptor reflex sensitivity as a result of weight loss.[17] This serves to emphasize the importance of weight loss for overall health in overweight persons with OSA.

In summary, studies to date demonstrate that weight loss, achieved by dietary modification can occur and can be significant. The effects of weight loss on oxyhemoglobin desaturation events are impressive. These data suggest that when a sufficient degree of weight loss is achieved, it will probably result in substantial improvement in OSA. Clearly, major advances in the effectiveness of dietary weight loss programs are needed to minimize obesity.

Peppard and coworkers analyzed a subset of participants in the Wisconsin Sleep Cohort in which baseline and follow-up polysomnograms were performed after a 4 year interval.[19] The relation between weight change and change in AHI was evaluated. Overall, a 10% weight reduction predicted a reduction in AHI by 26%. The degree to which weight change predicted a change in AHI was not influenced by the baseline AHI. As a non-interventional trial involving subjects with relatively mild OSA and in light of the fact that the cause of weight loss was not known, the findings may not be extrapolated to the general population of OSA patients.

The lack of prospective randomized studies of bariatric surgery is acknowledged, and the reported observations are considered in this light. A large case series examined pre- and post-operative polysomnographic data[20-22] and demonstrated improvement in metrics of sleep-disordered breathing following weight reduction, with reported alleviation of the need for medical therapy for OSA. Although the group AHI was significantly reduced, the

percentage of subjects in whom PAP therapy was discontinued and the percentage of subjects with AHI's <5 were not reported. One recent surgical series[22] demonstrated an overall improvement in sleep and breathing during polysomnography performed after an average of 13 months post-operatively. The degree of improvement varied within the study population, and there were subjects in whom OSA persisted despite a large degree of weight loss.[22] Of note, sleepiness, as assessed by the mean sleep latency on Multiple Sleep Latency Testing was not improved following weight loss, in spite of the improved AHI.[21,22] Concern is also raised by the results of two older studies indicating recurrence of OSA following initial improvement with weight loss in the absence of weight regain.[23,24] Patient selection and surgical procedures have improved, and most recent studies show that 10 years post-operatively, 40% of excess body weight is still gone.[25] It is evident that long-term assessments following weight reduction across the various surgical procedures (e.g. laparoscopic gastric banding, gastric bypass, etc.) are required to provide a more complete understanding of the benefits or limitations of these interventions. Finally, the issue of selection bias must be considered both in terms of who undergoes a procedure as well as when examining short and long-term longitudinal studies. When only a sub-set of the initial population is available for follow-up evaluation, the possibility of selection bias becomes a concern. Future studies must be designed to address this problem.

A meta-analysis of effects of bariatric surgery on co-morbidities (reported 1993-2000) found that OSA resolved in 87% of patients in whom studies were performed.[26] Although highly effective in the optimally selected patients, a national review found a significant complication rate of 10% from bariatric surgeries.[27] Most of these complications were problems in wound healing, anastomotic leaks, pneumonias, congestive heart failure and infection. It is equally important that anesthesiologists are experienced with upper airway management for the OSA patient undergoing bariatric surgery.[28]

3.2 PHARMACOLOGIC AGENTS

OSA is a sleep state-dependent disorder with generally normal ventilation and upper airway function during wakefulness. Theoretically, this sleep state-dependent breathing disorder should be readily amenable to pharmacotherapeutics targeting the state-dependent neurochemical changes. The approach to date has involved drug therapies which are putative ventilatory stimulants or REM sleep suppressants. Major study design flaws in currently reported drug trials include inadequate statistical power to detect differences of <50% in the AHI, and an under appreciation of the potential for night-to-night variability in AHI or in drug dose responses. Repeated observations and dose response studies are expected in future studies. Another limitation is that the study parameters usually include AHI but do not include neurobehavioral and cardiovascular outcomes, in contrast to the standards set by PAP studies.[1-3] Thus, at present, drugs should be considered as either second line therapies or as adjuvant therapies.

3.2.1 Serotoninergic Agents. The pharmacology involved in modifying the serotoninergic system is very complex. There are over 14 molecularly and pharmacologically distinct human serotonin receptor subtypes. Activation of some of these subtypes inhibits upper airway dilator activity and/or central ventilatory drive; while activation of other subtypes excite upper airway dilator motoneurons and/or central drive.[29] Moreover, a recent study shows that intermittent hypoxia, as a model for sleep apnea oxygenation patterns, alters the responsiveness of upper airway nerves to serotonin.[30] Thus, some serotoninergic agents might be beneficial while others might worsen sleep apnea, and subsets of patients could have different response patterns to serotoninergic therapies, depending on hypoxic exposure.

Selective serotonin reuptake inhibitors. Three studies have examined the role of selective serotonin reuptake inhibitors in the treatment of OSA.[31-33] One study examined the effects of 20 mg of fluoxetine for 4 weeks on the AHI in subjects with baseline indices ranging from 8 to 114 events/hour. The group AHI decreased from 57 to 34 events/hour, but this reduction did not achieve statistical significance, and the total number of oxyhemoglobin desaturations did not change with therapy.[31] Berry et al.,[33] examined the effects of single-dose paroxetine on AHI and genioglossus muscle activity. They found no effect of paroxetine on the AHI, but did find increased inspiratory muscle activity in the geneioglossus with therapy.[33] Kraiczi and colleagues conducted a double-blind, randomized, placebo-controlled trial of paroxetine for six weeks.[32] In this Level II study, paroxetine caused a statistically significant reduction in AHI, albeit the changes were small (AHI=36.3 ±24.7/hr mean±SD with placebo vs. 30.2 + 18.5/hr with paroxetine). Furthermore, paroxetine did not improve subjective sleepiness.[32]

Mirtazapine. At the time of this writing, there are no published clinical trials testing the effectiveness of mirtazapine on OSA. However, this drug has been shown to increase genioglossus activity in the rat.[34] Mirtazapine is a $5\text{-HT}_{2C \text{ and } 3}$ antagonist, with additional effects at noradrenergic and histaminergic receptors that may enhance central ventilatory drive through disinhibition of vagal-nucleus tractus solitarius ventilatory inputs. We mention mirtazapine in this report because it is important to appreciate that there are significant concerns that must be addressed before prescribing this drug for OSA. Specifically, increased subjective sleepiness and weight gain have been documented in many subjects using this agent.[35]

3.2.2 REM sleep suppressant therapy. There are subsets of patients who experience obstructive apnea and hypopnea events almost exclusively in REM sleep. Although these patients would be the most appropriate subset in which to test the effectiveness of REM suppressant therapies, the effectiveness of REM sleep suppressant therapy in these individuals has not been determined. Fluoxetine and paroxetine, listed in the above section, also have significant REM sleep suppressant effects. Whether REM sleep suppressant therapies continue to suppress REM sleep long-term, for example across months or years of therapy, has not been fully determined.

Protriptyline. Protriptyline is a tricyclic antidepressant with noradrenergic and serotoninergic reuptake inhibition in addition to anti-cholinergic effects. Randomized, double-blind, placebo-controlled trials of protriptyline, a non-sedating tricyclic antidepressant, have been performed involving sample sizes of 5-10 subjects.[31,36-39] Two of the studies showed some benefit with protriptyline. In the earlier study[39] examining the effects of protriptyline in 11 male and one female adult subjects with very severe OSA (AHI's ranging from 50-100), the NREM sleep AHI for the group fell from 74 to 53, $p<0.05$, and 10 of the 12 subjects ex-

perienced subjective improvement. Another important finding in this study was the significant effect of protriptyline on the magnitude of oxyhemoglobin desaturations from 17% to 9%, p<0.001 (39). REM sleep was suppressed from 9% to 4%, p<0.001; yet the frequency and severity of REM sleep events was unchanged.[39] A second study also found improvement in the frequency of NREMS AHI (57 vs 33, p<0.05 and improvement in nocturnal oxygenation.[31] A third trial also found that protriptyline improved oxygen saturation during sleep but produced no change in the apnea or hypopnea indices.[36] A fourth trial in which protriptyline was administered for a shorter period prior to polysomnography (1 vs 2-4 wks of therapy) found no effect on either oxygenation or AHI.[38] Despite anti-cholinergic side effects many subjects in the first three studies experienced significant subjective improvement in sleepiness.

In conclusion, while protriptyline may reduce sleepiness and the AHI, there is insufficient improvment in the AHI to justify use of protriptyline as a therapy for OSA.

*Clonidin*e. There is one study reported in the English literature evaluating the effectiveness of clonidine, a noradrenergic alpha 2 agonist. The rationale for testing this drug was its REM sleep suppressant effect. The REM sleep suppressant effect is relatively weak, however, and clonidine has been shown to hyperpolarize hypoglossal motoneurons[40] and produce upper airway occlusions with systemic administration.[41] The one clinical trial of clonidine that was reviewed included 8 men, in 2 of whom there was no effect on REM sleep.[39] In the other six subjects, REM sleep was reduced by 30-40%. The severity of hypoxemia in these six subjects was improved; however, in two of these six subjects hypopneas were converted into apneas.[42]

3.2.3 Ventilatory Stimulants

Methylxanthine derivatives. There have been four reports on the effectiveness of methylxanthine drugs on OSA.[43-46] One study examined the overnight effects of acute dosing of intravenous aminophylline on 10 males with moderate-severe OSA.[43] Intravenous aminophylline improved the frequency of central events (although rare, 4/hr), but did not affect obstructive events, AHI=32±6/hr (mean±SE) on placebo and 29±9/hr on aminophylline.[43] One important side effect was that sleep efficiency dropped by over 25%.[43] There are three studies examining the effectiveness of theophylline on OSA.[44-46] These are all Level II studies: randomized controlled trials with small sample sizes (n=12-14 subjects). Two of the studies observed small but statistically significant improvements in the AHI (from 49 to 40[44] and from 29 to 20[45]). The third study found no measurable defect, but this was a smaller study employing portable monitoring equipment.[46] Important adverse events included reductions in sleep efficiency and total sleep time in all studies.

Opioid antagonists. Three studies have examined the effects of intravenous naloxone on the abnormal breathing in subjects with OSA. However, none of the reports examined the effects of drug on the AHI. In one study the index of >4% oxyhemoglobin desaturations fell from 22 to 19 events/hr.[47] All naloxone studies reported reduced sleep efficiency and increased awakenings.

Doxapram. There is one Level III study examining the effects of doxapram on OSA on 4 male subjects measuring the minimal oxygenation and average length of hypopneas.[48] AHI was not determined in this study. Oxygenation improved and the duration of hypopneas was shortened. Side effects were not described.[48] However, doxapram requires continuous intravenous infusion, and is contraindicated in persons with epilepsy, ischemic heart disease, hyperthyroidism or severe hypertension. In summary, there are significant practical limitations for use of this particular drug.

Nicotine. The pharmacology of nicotinic agents is complex with multiple muscarinic and nicotinic subtypes. As is the case with the serotoninergic subtypes, select muscarinic and nicotinic receptor subtype agonists may have opposing effects on ventilation, behavioral state and motoneuronal control. Three papers have reported effects of nicotine therapy on OSA. While an initial case series[49] suggested that nicotine reduced apnea index during the early hours of sleep from 85 =7 to 62±7, p<0.05, at 2 hrs into therapy, two ensuing publications did not show an effect. Davila and colleagues[50] published a report of efficacy of a nicotine patch administered in a randomized, double blind, crossover design with a placebo patch to 20 OSA subjects. These investigators reported that nausea, reduced total sleep time, reduced sleep efficiency, and percent REM sleep were common side effects from this therapy, and that nicotine had no significant effect on the AHI. Zevin and associates[51] studied 11 subjects with OSA in a randomized, double-blind, cross-over fashion with nicotine at 2 and 4 mg, as administered via an oral patch. Nicotine administration was associated with prolonged latency to sleep and increased percentage of time spent in Stage 1, without a favorable effect on the AHI.[51] The authors concluded that locally delivered nicotine at these doses had no effect on OSA. As this was a randomized, double blind, crossover study (albeit with no placebo), this study was accorded Evidence Level II.

3.2.4 Endocrinological disorders and conditions predisposing to sleep apnea

Thyroid hormone replacement therapy. In patients with overt hypothyroidism, thyroid replacement hormone may, over time, completely reverse OSA. Two studies were reviewed that examined the effects of thyroid hormone replacement on the AHI in persons with OSA. One of these is a small case series, in which thyroid replacement therapy improved the AHI to normal values in two patients and by >50% in a third.[52] The second study examined 11 patients before and after thyroid replacement therapy but before weight loss following thyroid replacement.[53] In this study, the AHI fell overall from 72 to 12, p<0.001. Thus, all persons presenting with OSA should be evaluated by history and physical exam for signs and symptoms of hypothyroidism, and treated if clinical suspicion is confirmed with appropriate blood tests. In light of the potential to precipitate organ ischemia if thyroid replacement therapy augments the metabolic rate and oxygen consumption prior to alleviating OSA, patients should be treated with positive airway pressure until the OSA has been documented to be fully reversed. Reversal of hypothyroidism-induced OSA may take over one year, and pressures may need to be adjusted over the course of therapy.

Growth hormone suppressant therapy for acromegaly. There have been two reports examining the effectiveness of treating acromegaly on the AHI. One is a case series of 10 subjects using bromocriptine, where the percentage of sleep time spent in apnea and hypopnea dropped by 75%.[54] The second study examined octreotide, a somatostatin analog, and reported significant reduction in the AHI from 39 to 19 events/hr, p<0.0001.[55] For this reason, it is imperative to evaluate all patients presenting with OSA for

acromegaly, by history and physical exam, and if suspected, the appropriate endocrine evaluation should be pursued. Treating the underlying endocrinological disorder is expected to significantly improve the severity of OSA.

Medroxyprogesterone and estrogen therapy. Although menopause is an independent risk factor for OSA, a randomized prospective study examining the effects of hormonal replacement therapy on the prevention of OSA has not been performed. There are seven studies examining OSA and estrogen and progesterone supplementation in postmenopausal women.[56-62] Both estrogen and progesterone enhance ventilatory chemosensitivity, and may partly offset the sleep state-dependent reductions in ventilatory drive that may contribute to the pathogenesis of OSA.[63] One week of medroxyprogesterone and conjugated estrogen therapy in women with mild OSA and previous bilateral ovariectomy and hysterectomy resulted in significant reductions in obstructive events.[56] A smaller study identified reductions in apnea frequency with estrogen and progesterone supplementation.[57] The effect of hormonal therapy on hypopneas was not reported.[57] A third study of 6 post-menopausal women found a reduction in the AHI from 25 to 12 events, $p<0.01$, with estrogen alone therapy.[58] In this study, supplementation with progesterone was of no additional benefit, and may have worsened the apnea frequency in a subset of the subjects.[58] A randomized, placebo-controlled trial of 51 post-menopausal subjects found a positive effect of estrogen and/or progesterone (as estradiol valerate with or without the progestogen dienogest) on the AHI.[59] In this study, women experienced an overall improvement in the AHI on the combined therapy but not on estrogen alone. However, three studies have shown seemingly contradictory findings, with no effects of estrogen and/or progesterone on AHI in post-menopausal subjects with moderate-severe OSA.[59-61] In a larger (n=62) randomized controlled crossover trial, estrogen therapy had minimal effects on apneas and upper airways resistance events in post-menopausal women.[62]

Whether these discrepancies in effect of hormonal replacement therapies represent differences in drugs and doses, sample sizes, severity of OSA, age of women, or physical differences cannot be determined from the reviewed studies. However, without an obvious benefit of hormonal replacement therapy for OSA and with an increasingly recognized number of adverse effects, hormonal replacement therapy solely for the treatment of OSA in postmenopausal women cannot be justified.

Three studies have examined the effectiveness of medroxyprogesterone in males with OSA, and in these studies (both Level III), no significant effects on apnea index were observed. [64-66]

Androgen blockade and testosterone replacement therapy. There is one study examining the effects of androgen blockade with flutamide on the AHI in persons with OSA.[67] The study found no significant difference with therapy. A second study examined whether acute administration of testosterone had adverse effects on the AHI in persons with OSA, with the finding of a 50% increase in AHI and greater hypoxemia.[68]

Wake-promoting substances. Many patients demonstrate residual sleepiness despite effective therapy with nasal CPAP.[69] The stimulant modafinil has been investigated as an adjunctive therapy for residual sleepiness.[70-75] This drug has no effect on the AHI,[71,72] but has been shown to reduce objective sleepiness by approximately one minute.[70-75] Six prospective studies report the effects of modafinil on daytime sleepiness in OSA patients. Five studies have reported the effects of modafinil (200 to 400 mg/day) on residual sleepiness in subjects with OSA, despite compliance with CPAP.[70-72,74,75] Modafinil consistently (across studies) improved subjective and objective sleepiness, quality of life and vigilance compared to placebo. It is important to appreciate, however, that the vast majority (75%) of subjects with severe sleepiness at baseline still had multiple sleep latency times of <10 min on modafinil, despite effective CPAP and good compliance with therapy. Therefore, prescribing modafinil should not lessen the concerns of continued risk for sleepiness and driving-related motor vehicle accidents related to sleepiness in patients with OSA. Clearly, this is an important area in need of further study.

The adverse events attributed to modafinil include headaches, nervousness and rhinitis (5-10% higher likelihood than placebo). A two-week, placebo-controlled study with one dose (400 mg) of modafinil[72] demonstrated that patients using this stimulant had a modest but significant reduction in their nightly usage of nasal CPAP. This negative effect was not found in the other two double-blind studies of longer duration[71,72] or in the open-label continuation study (75).

Acute administration of modafinil increases arterial blood pressure and heart rate.[73] With exercise, modafinil intake (300 mg) results in a significant increase in mean systolic and diastolic pressures as well as heart rate compared to placebo. No long-term investigation of cardiovascular outcomes with the use of modafinil has been reported.

In summary, the double-blind, placebo-controlled clinical trials which examined the effectiveness of modafinil in patients compliant with nasal CPAP in treating residual sleepiness found that modafinil subjectively and objectively improved vigilance and sleepiness for as long as 12 weeks. However, modafinil does not fully reverse severe baseline sleepiness. It appears that 200 mg daily is as efficacious as 400 mg. There is a concern that compliance with CPAP may fall with modafinil usage,[72] and this requires further study. In the interim, patients must be advised of the importance of continuing PAP therapies and physicians must carefully monitor PAP compliance in this group. The question of the long-term effect of modafinil on the hemodynamic status of OSA patients treated with nasal CPAP remains unresolved. Nevertheless, findings from one study measuring cardiovascular responses to modafinil raise the possibility that modafinil use may increase blood pressure.[73] Thus, careful consideration of an individual patient's health risks (motor vehicle accidents vs. cardiovascular morbidities) is required prior to prescribing modafinil. Patients should be advised of the likelihood of continued sleepiness during driving and that the risk for modafinil-related cardiovascular adverse events is simply not known.

3.3 Supplemental Oxygen

There have been four randomized controlled trials of supplemental oxygen therapy for OSA.[76-79] Although sample sizes in all four studies are small, a consistent finding is a reduction in the severity of hypoxemia. The sleep-related oxyhemoglobin saturation nadir improved on oxygen, and in the one study where hypopneas were examined separately from apneas, a reduced hypopnea index was identified. Two of the supplemental oxygen trials examined the effectiveness of transtracheal supplemental oxygen,[76,77] and one found a significant reduction in the AHI from 65 to 26, $p<0.05$[72] and trended towards a reduction in the other study with just 4 subjects.[77] Of the remaining two studies in which supplemental oxygen was administered nasally to adults with obstructive sleep apnea, the minimum oxyhemoglobin saturation significantly improved in both studies. Importantly, subjects noted less sleepiness with supplemental oxygen.[78,79] One of the future directions needed to characterize the effectiveness of supplemental ox-

ygen in persons with OSA is to perform randomized placebo-controlled crossover trials characterizing oxygen dose-responses in individual subjects. This is essential to distinguish night-to night variance in AHI from true responses in individual subjects and to identify the optimal oxygen level for therapy in a given patient.

3.4 Medical Therapies Intended to Improve Nasal Patency

Two papers report on the effectiveness of nasal spray decongestants and corticosteroids on obstructive sleep apnea and qualified for inclusion this review. Braver and Block[80] reported a randomized, controlled trial in 20 males with obstructive sleep apnea. They conducted comparisons between the administration of oxymetazoline nasal spray to each nostril before bedtime by itself, in combination with a "best sleep posture", and with sleeping in the "best sleep posture" alone. This study suggested that postural therapy alone and in combination with oxymetazoline nasal spray significantly reduced AHI, but oxymetazoline nasal spray alone had no effect. The findings from this study, therefore, suggest that this short-acting nasal decongestant with an established rebound rhinorrhea later in the night may not be an effective therapy in all OSA patients. This report was a randomized, controlled trial and was assigned Evidence Level II.

Kiely and associates reported the effects of inhaled corticosteroids on the AHI in 23 adults with OSA and coexisting rhinitis.[81] These patients were assigned in a double-blind, randomized order to fluticasone nasal spray 100μg or placebo twice daily for 4 weeks, followed by a cross-over to the alternative arm. While subjects were on fluticasone, their mean AHI was reduced to 12 events/hr, in comparison to 20 events/hr on placebo ($p<0.05$). There was also a reduction in nasal resistance, but no change in oxygenation, subjective sleepiness or sleep quality for subjects with AHI's >10 events/hr.[81] This study was assigned Evidence Level I. In conclusion, patients with nasal congestion may benefit from nasal corticosteroids, but it is unlikely that this therapy alone would sufficiently treat OSA.

3.5 Positional Therapies

Five studies meeting review criteria considered the effects of supine vs. side posture, elevated head posture, and specially designed pillows.[82-86]

Jokic and colleagues examined the effectiveness of lateral positioning therapy compared with PAP using a randomized, single-blind crossover trial in 13 male subjects with mild-moderate OSA.[82] Positional therapy, relative to baseline, improved the AHI by 8 events/hour, $p<0.01$. (The mean difference in the decline in AHI was 6 between positional therapy and CPAP; but positional therapy itself decreased the AHI by 8 events/hr (from 17.9 to 9.5). PAP provided greater improvements in AHI and minimum oxyhemoglobin saturation compared to positional therapy. In another study,[85] lateral posture, achieved either through a posture alarm or simple instructions, resulted in similar reductions in AHI compared to the use of a tongue retaining device.

In a more recent study,[83] the effect of upright posture during sleep on OSA was examined. This randomized crossover trial of adult males with mild to severe OSA compared the effectiveness of PAP and upright posture on the AHI. The group AHI decreased from 27 to 21 events/hr with upright posture, which was not statistically significant. In contrast, PAP was effective in 12 of the same 14 subjects. Whether upright posturing is beneficial in a subset of individuals will require further study.

The effects of specially designed pillows to improve neck and body position in sleep have been examined. One of these is a triangular pillow that positions both the neck and upper body.[86] In a Level III (the study was a nonrandomized controlled study; cervical pillow versus control nights were nonrandomized) study of adults with mild to moderate OSA, use of the pillow was associated with an overall reduction in the AHI by 17 events/hr, $p<0.0001$. Snoring was reduced or eliminated and the oxyhemoglobin saturation improved. In another pillow study examining the effects of cervical position, Kushida et al., found improvements in the AHI in subjects with mild OSA, but no effect in individuals with more severe apnea.[84] In a follow up study of 18 patients with mild to moderate OSA, the same authors showed that this cervical pillow decreased the AHI by 4 events/hr.[84] These pillows are patented or have patents pending, and are intended for over-the-counter use. Although both studies show promise, the findings must now be replicated in larger randomized independent studies with a placebo pillow (one that allows full neck/body movement) serving as the control condition. The use of such pillows should also be subject to more rigorous outcome and comparison studies, as the cost-risk ratio for the use of such adjuncts to behavioral advice would be favorable for those in whom other treatments (CPAP, surgery, or oral appliance) are either not indicated or poorly tolerated. As these positional devices may become publicly available and advertised, independent information on their clinical utility would inform physicians, patients, and the general public about the appropriateness and efficacy of this approach alone, in combination, or compared to other treatment options.

4.0 CONCLUSIONS

Several practical conclusions may be drawn from this body of literature. First, weight loss through application of a low calorie diet can result in sufficient weight loss to improve OSA, and is recommended as an adjunctive therapy for all overweight individuals with OSA. Moreover, sufficient weight loss is expected to substantially reduce the AHI in most patients. Both additional and longitudinal studies of surgical weight reduction in OSA patients are required to assess long-term outcome, adverse events and to define optimal peri- and post-operative management in this population. Second, hypothyroidism and acromegaly are two endocrinological disorders that should be routinely screened for through history and physical exam in the sleep clinic. When these disorders are treated, OSA may be significantly improved or even reversed. The third point is more discouraging. Despite numerous drug trials, few conclusions can be drawn largely because of study design limitations and insufficient knowledge of the neurochemical mechanisms through which sleep places the upper airway at risk for collapse. Moreover, drug trials have not examined cardiovascular and neurobehavioral end points. Oxygen therapy may be helpful in patients who decline the opportunity to use CPAP, but presently it is uncertain which patients will benefit from supplemental oxygen, what the optimal dose is, and what the long-term consequences and benefits of supplemental oxygen use are.

A successful future for novel medical therapies will depend upon the execution of well-controlled, adequately powered studies that examine not only effects on the AHI but also on all health related outcomes shown beneficial with PAP therapy.

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