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PRO/CON DEBATE

Mild Obstructive Sleep Apnea Syndrome Should be Treated

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What little I remember from high school concerning debating technique consists of the Jesuit adage, "define your terms." Consequently, I will begin by reviewing the possible criteria by which obstructive sleep apnea (OSA) could be considered "mild" in degree. The various attributes attached to OSA include the presence of symptoms (most frequently, hypersomnia), as well as various metrics obtained from the overnight polysomnogram. The latter include degree of oxyhemoglobin desaturation, which might encompass saturation nadir, total sleep time (TST) below a certain saturation, or mean saturation; respiratory-associated arousal index; or apnea-hypopnea index (AHI). Although the definition of "mild" OSA could be the subject of its own debate, the American Academy of Sleep Medicine has, in fact, taken a position on this issue.[1] Two criteria are used: sleepiness, which must be either absent or mild in degree (only occurring in sedentary situations), and AHI, which must fall between 5 and 15 events per hour of sleep. Unfortunately, mild OSA in clinical research has almost universally been defined only in terms of AHI, usually that in the range of 5–15. This definition must then suffice for purposes of this debate.

Having defined mild OSA, I will frame my argument for treating this degree of sleep apnea by outlining the evidence that: (1) Mild OSA can cause symptoms; (2) Mild OSA can lead to adverse sequelae; (3) Mild OSA can be treated; and (4) Treating mild OSA can lead to improved outcomes. Fortunately, there are now several population studies that can aid us in this endeavor. With respect to symptoms, data from the Sleep Heart Health Study[2] have demonstrated a significant relationship between AHI and sleepiness as measured by the Epworth Sleepiness Scale (ESS).[3] When compared to subjects with AHI <5, mean ESS values rose steadily as OSA severity category increased from "minimal" to "severe"; with sleepiness defined as ESS ≥11, 28% of subjects with AHI between 5 and 15 were sleepy compared to 21% of those with AHI <5.[2] Data from the Wisconsin Sleep Cohort Study are even more intriguing: subjects with snoring but AHI <5, presumably a degree of sleep disordered breathing considerably less than "mild," had significantly more complaints of excessive daytime sleepiness, awakening feeling unrefreshed, and uncontrollable sleepiness interfering with life (all ≥2 days/week) compared with nonsnoring controls.[4] The Sleep Heart Health Study has also demonstrated a significant worsening of quality of life in subjects with mild OSA.[5] Compared with controls, the odds ratio for subjects with AHI between 5 and 15 reporting a poor quality of life on the Medical Outcomes Study 36-item Short-Form health survey (SF-36)[6] Vitality Scale was 1.20 (95% confidence interval or CI, 1.02–1.43).

The same two population studies (Sleep Heart Health and Wisconsin Sleep Cohort) have provided important information linking mild OSA with adverse cardiovascular and metabolic outcomes. Cross sectional data from the former study demonstrated a linear relationship between blood pressure and AHI starting with the most minor degree of severity: prevalence of hypertension was 43% for AHI <1.5, 53% for AHI between 1.5 and 4.9, and 59% for AHI between 5 and 14.9; this relationship held even after adjustment for body mass index (BMI).[7] Prospective data from the Wisconsin Sleep Cohort have proven an even stronger relationship in terms of 4-year incidence of developing hypertension: compared to subjects with AHI=0, odds ratios (and 95% confidence intervals) for incident hypertension were 1.42 (1.13-1.78) for AHI between 0.1 and 4.9 and 2.03 (1.29 - 3.17) for AHI between 5 and 14.9.[8] The same investigators had previously demonstrated a cross-sectional prevalence relationship,[9] as have several other groups analyzing other populations.[10,11]

Similar results have been obtained in cross-sectional investigations of cardiovascular disease prevalence. The Sleep Heart Health Study demonstrated a "modest and significant linear" relationship between relative odds of cardiovascular disease (coronary heart disease, heart failure, and stroke) and quartile of AHI, starting with the mildest quartile (AHI = 1.4–4.4).[12] Few studies are available thus far examining incident risk of cardiovascular disease in OSA, and none include a well-characterized group with mild OSA. For instance, Peker et al reported prospective data from a group of 182 middle-aged men from the Gothenburg Sleep Clinic Cohort who entered the study without cardiovascular disease.[13] Patients with incompletely-treated OSA had more incident cardiovascular events than controls after 7 years of follow-up, but OSA severity was not accurately measured by today's standards: oxygen desaturation index in the OSA group was 16.5 ± 15.3 (mean ± standard deviation or SD), suggesting a predomi-

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nantly mild-moderate level of disease. Also, Marin and colleagues published prospective observational data on 403 patients with untreated mild to moderate OSA (AHI between 5 and 30) compared to 264 controls, and demonstrated a tendency toward increased fatal and non-fatal cardiovascular events in the patient group after about 9 years of follow-up.[14] It is hoped that future publications from the Wisconsin Sleep Cohort, the Sleep Heart Health Study, or other ongoing prospective studies will provide more information on this issue.

Three reports illustrate a possible association between insulin resistance/glucose intolerance and mild OSA. One examined a subset (n= 2,656) of the Sleep Heart Health Study in which all enrollees had fasting blood glucose determinations, followed by a 75 gm glucose challenge and 2-hour glucose determination in 1,930 of the subjects.[15] Adjusted odds ratio for elevated fasting glucose (as a marker of glucose intolerance) was 1.27 (95% CI, 0.98–1.64) for subjects with AHI between 5 and 15 compared with controls (AHI <5), and there was a significant overall trend with increasing severity of AHI. The odds ratio for an abnormal 2-hour glucose was 0.88 (95% CI, 0.88-1.35) in the mild OSA group, but again with a significant overall trend. The second study, by Ip and coworkers, examined fasting insulin levels and homeostasis model assessment method (HOMA-IR) as indices of insulin resistance in 270 patients.[16] All were referred for evaluation of possible OSA and none had a history of physician-diagnosed diabetes. Using multiple linear regression, they demonstrated that AHI was an independent determinant of insulin resistance in both obese and lean subjects. The last study examined 4-year incident diabetes mellitus in 978 subjects from the Wisconsin Sleep Cohort.[17] The odds ratio for developing diabetes for subjects with AHI between 5 and 15, compared to those with AHI <5, was 1.83 (95% CI, 1.07–3.11) when adjusted for sex and age; when adjusted for sex, age, and waist girth, statistical significance was lost (odds ratio, 1.25; 95% CI, 0.75–2.07). However, there is a known relationship between visceral fat (and thus waist girth) and OSA;[18] furthermore, visceral fat is known to regress after OSA is treated.[19] Consequently, adjusting for waist girth in this study may actually have obscured a bona fide relationship to incident diabetes.

Supporting evidence that is not epidemiological in nature is also available. Three small studies of carotid artery sonographic markers of early atherosclerosis have demonstrated abnormalities in mild OSA. All defined mild severity as an AHI between 5 and 19; observed AHI was 12.9 ± 3.8 (mean ± SD) in one study,[20] 11.0 ± 0.9 (mean ± standard error of the mean, or SEM) in the second,[21] and 16.2 ± 1.7 (mean ± SD) in the third,[22] thereby largely adhering to my working definition of mild OSA. The latter study also demonstrated differences in a separate index of early atherosclerosis, carotid-femoral pulse wave velocity.[22] Most recently, Duchna and coworkers studied 10 normal controls and 10 patients with mild OSA (AHI between 5 and 15) with respect to maximum endothelium-dependent vasodilation to bradykinin.[23] This index of early vascular endothelium dysfunction was abnormal in mild OSA compared to controls, and significantly improved after CPAP treatment in 7 of the mild OSA patients. Finally, one large-scale investigation derived from the Sleep Heart Health Study examined 1,037 elderly subjects by means of sonographic measurement of baseline brachial artery diameter and percentage of flow-mediated dilation.[24] A dose-response relationship was present between both measures of endothelial dysfunction and AHI when corrected for demographic variables, starting with the mildest degree of OSA. However, these relationships were not significant when adjustment was added for BMI and serum cholesterol.

The issue of whether mild OSA is treatable can be dealt with in short order. "Life-style" treatments such as weight loss and avoidance of alcohol and respiratory depressant drugs near to bedtime have an adjunctive role, but are not considered primary therapeutic modalities.[25] Sleep position training in those individuals shown to have significant OSA only when supine is usually easily accomplished (unless musculoskeletal disease makes non-supine sleep too uncomfortable) and effective.[25-27] Mandibular advancement devices have proven to be viable options in treating mild OSA, with perhaps no single issue in sleep medicine having been subjected to as many systematic reviews and meta-analyses as this therapeutic modality. These include 1995 and 2005 reviews and practice parameters by the American Academy of Sleep Medicine,[28-31] a Cochrane Collaboration review,[32] and systematic reviews by Hoekema et al,[33] Ng et al,[34] and Hoffstein.[35] All analyses indicate that mandibular advancement devices are appropriate for the treatment of mild OSA as long as efficacy is verified in any individual patient, and that self-reported compliance with treatment is high (frequently higher than with positive airway pressure treatment). Conventional surgical treatment of OSA incorporates uvulopalatopharyngoplasty for oropharyngeal obstruction with or without base-of-tongue procedure(s) meant to address hypopharyngeal obstruction. Practice parameters and a review by the American Academy of Sleep Medicine some 10 years ago did not support the routine use of these procedures for OSA treatment,[36,37] and a recent Cochrane Collaboration review sustained that recommendation.[38] A thorough discussion of surgery for mild OSA is beyond the scope of this paper, save to note that it can be efficacious in some patients and thereby obviates the need to assess compliance. Finally, positive airway pressure (PAP) remains the reference standard for OSA treatment in that significant amelioration of obstructive respiratory events is virtually guaranteed as long as the device is actually worn.[39] Patients with mild OSA, particularly those who are asymptomatic, can

Table 1—Compliance with positive airway pressure treatment in mild to moderate OSA.

Reference number	N	AHI	Follow-up Time	Compliance, hours/night	Compliance, Other Metric
41	29	21.6 ± 7.5[a]	3 weeks	4.9 (0-8.4)[b]	62% of nights with >4 hours
42	88	21.3 ± 1.3[c]	3 months	3.6 ± 0.3[c]	43% with ≥4 hours use for 70% of nights
43	28	12.9 ± 6.3[a]	8 weeks	3.53 ± 2.13[a]	48% with >4 hours use/night
44	48	31 ± 26[a]	2 months	4.9 ± 2.4[a]	n/a
45	66	20 ± 6[a]	6 months	4.8 ± 2.2[a]	64% with >4 hours use/night

[a]standard deviation; [b]range; [c]standard error of the mean.

be significantly less inclined to use their PAP device compared with individuals with more severe, or more symptomatic, OSA.[40] However, multiple clinical trials in patients with relatively mild degrees of OSA have still shown that substantial compliance is likely (Table 1).[41-45] Given the availability of these multiple effective treatment modalities, it seems clear that mild OSA can be treated in most patients.

The final issue is that of whether treatment of mild OSA measurably improves outcome. Thus far, virtually all reports investigating the efficacy of treating milder degrees of OSA have focused on continuous PAP (CPAP) as the treatment modality, and hypersomnia as the measured outcome. There are 7 studies that have used ESS score as an outcome metric: 2 compared CPAP to conservative treatment[45,47] (neither was a crossover trial), and 5 were placebo controlled[41-43,46,48] (4- placebo medication, 1- sham CPAP). All but one of the latter studies used a crossover design. Subject enrollment ranged from 16 to 125, with a median study population of 34 and a total number of subjects across all studies of 409. Two studies, for a total of 50 patients, required an AHI of 5–15 for enrollment;[46,48] 4 studies enrolled subjects with AHI of 5–30;[41-43,47] one study limited AHI to 10–30.[45] Marshall and colleagues have published a meta-analysis of pooled data from these 7 reports and found a significant improvement in ESS score (a reduction of 1.2 points; 95% CI = 0.5–1.9, p = 0.001) comparing placebo/conservative treatment to active treatment.[49] Three of these studies also performed maintenance of wakefulness tests,[41,42,48] and the meta-analysis of pooled data from these reports revealed a significant increase in mean sleep latency on active treatment of 2.1 minutes (95% CI, 0.5–3.7; p = 0.011).[49] It is also instructive to examine more closely the 2 trials that concentrated on the mildest degree of OSA (AHI between 5 and 15), those by Engleman and colleagues.[46,48] The first of these, a pilot study of 16 patients, demonstrated no significant improvement in sleepiness, but improvement in a measure of quality of life in the subjects with best CPAP compliance.[46] The second study examined a new group of 34 subjects in a placebo-controlled crossover design.[48] An average CPAP use of 2.8 hours/night resulted in significant improvements in ESS score (11 ± 4 points on placebo vs. 8 ± 4 points on CPAP, p = 0.008); 2 tests of cognitive performance (Digit Symbol Substitution subtest of the Wechsler Intelligence Scale-Revised, and the Paced Auditory Serial Addition Test); and multiple tests of psychological well-being, health, and functional status (Hospital Anxiety and Depression Scale- depression, SF-36 Health Transition, Role- Physical, Bodily Pain, Social Function, and Vitality scales).

In conclusion, the accumulating literature on mild OSA (as defined by an AHI between 5 and 15) provides clear evidence that disease of this modest severity can be symptomatic, can lead to adverse consequences, can be treated, and that such treatment will lead to improvement in some outcomes. The fact that these improved outcomes relate particularly to patient quality of life leads me to conclude that treatment is indeed beneficial even in mild OSA and should be pursued.

REFERENCES

1. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667-89.
2. Gottlieb DJ, Whitney CW, Bonekat WH, et al. Relation of sleepiness to respiratory disturbance index. The Sleep Heart Health Study. Am J Respir Crit Care Med 1999;159:502-7.
3. Johns MW. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep 1991;14:540-5.
4. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230-5.
5. Baldwin CM, Griffith KA, Nieto J, et al. The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. Sleep 2001;24:96-105.
6. Stewart AL, Hays RD, Ware JE. The MOS short-form general health survey: reliability and validity in a patient population. Med Care 1988;26:724-35.
7. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. JAMA 2000;283:1829-36.
8. Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378-84.
9. Young T, Peppard P, Palta M, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. Arch Intern Med 1997;157:1746-52.
10. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. BMJ 2000;320:479-82.
11. Bixler EO, Vgontzas AN, Lin HM et al. Association of hypertension and sleep-disordered breathing. Arch Intern Med 2000;160:2289-95.
12. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease. Cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001;163:19-25.
13. Peker Y, Hedner J, Norum J, et al. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea. A 7-year follow-up. Am J Respir Crit Care Med 2002;166:159-65.
14. Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005;365:1046-53.
15. Punjabi NM, Shahar E, Redline S, et al. Sleep-disordered breathing, glucose intolerance, and insulin resistance. The Sleep Heart Health Study. Am J Epidemiol 2004;160:521-30.
16. Ip MSM, Lam B, Ng MMT, et al. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002;165:670-6.
17. Reichmuth KJ, Austin D, Skatrud JB, et al. Association of sleep apnea and type II diabetes. A population-based study. Am J Respir Crit Care Med 2005;172:1590-5.
18. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000;85:1151-8.
19. Chin K, Shimizu K, Nakamura T, et al. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. Circulation 1999;100:706-12.
20. Altun R, Özdemir H, Mahmutyazicioğlu K, et al. Evaluation of carotid artery wall thickness with high-resolution sonography in obstructive sleep apnea syndrome. J Clin Ultrasound 2005;33:80-6.
21. Minoguchi K, Yokoe T, Tazaki T, et al. Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. Am J Respir Crit Care Med 2005;172:625-30.
22. Drager LF, Bortolotto LA, Lorenzi MC, et al. Early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med 2005;172:613-8.
23. Duchna H-W, Stoohs R, Guilleminault C, et al. Vascular endothelial dysfunction in patients with mild obstructive sleep apnea syndrome. Wien Med Wochenschr 2006; 156:596-604.
24. Nieto FJ, Herrington DM, Redline S, et al. Sleep apnea and markers of vascular endothelial function in a large community sample of

older adults. Am J Respir Crit Care Med 2004;169:354-60.
25. Morgenthaler TI, Kapen S, Lee-Chiong T et al. Practice parameters for the medical therapy of obstructive sleep apnea. Sleep 2006;29:1031-35.
26. Cartwright R, Ristanovic R, Diaz F, et al. A comparative study of treatments for positional sleep apnea. Sleep 1991;14:546-52.
27. Jokic R, Klimaszewski A, Crossley M, et al. Positional treatment vs continuous positive airway pressure in patients with positional obstructive sleep apnea syndrome. Chest 1999;115:771-81.
28. Schmidt-Nowara W, Lowe A, Wiegand L, et al. Oral appliances for the treatment of snoring and obstructive sleep apnea: a review. Sleep 1995;18:501-10.
29. American Sleep Disorders Association. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances. Sleep 1995;18:511-3.
30. Ferguson KA, Cartwright R, Rogers R, et al. Oral appliances for snoring and obstructive sleep apnea. Sleep 2006;29:244-62.
31. Kushida CA, Morgenthaler TI, Littner MR, et al. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: an update for 2005. Sleep 2006;29:240-3.
32. Lim J, Lasserson TJ, Fleetham J, et al. Oral appliances for obstructive sleep apnoea. Cochrane Database of Systematic Reviews 2006;CD004435:1-44
33. Hoekema A, Stegenga B, de Bont LGM. Efficacy and co-morbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review. Crit Rev Oral Biol Med 2004;15:137-55.
34. Ng A, Gotsopoulos H, Darendeliler AM, et al. Oral appliance therapy for obstructive sleep apnea. Treat Respir Med 2005;4:409-22.
35. Hoffstein V. Review of oral appliances for treatment of sleep-disordered breathing. Sleep Breath 2007;11:1-22.
36. Standards of Practice Committee of the American Sleep Disorders Association. Practice parameters for the treatment of obstructive sleep apnea in adults: the efficacy of surgical modifications of the upper airway. Sleep 1996;19:152-5.
37. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. Sleep 1996;19:156-177.
38. Sundaram S, Bridgman SA, Lim J, et al. Surgery for obstructive sleep apnoea. Cochrane Database of Systematic Reviews 2005;CD001004:1-45.
39. Gay P, Weaver T, Loube D, et al. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. A review by the positive airway pressure task force of the standards of practice committee of the American Academy of Sleep Medicine. Sleep 2006;29:381-401.
40. Krieger J, Kurtz D, Petiau C, et al. Long-term compliance with CPAP therapy in obstructive sleep apnea patients and in snorers. Sleep 1996;19(Suppl):S136-43.
41. Marshall NS, Neill AM, Campbell AJ, et al. Randomised controlled crossover trial of humidified continuous positive airway pressure in mild obstructive sleep apnoea. Thorax 2005;60:427-32.
42. Barnes M, McEvoy RD, Banks S, et al. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. Am J Respir Crit Care Med 2004;170:656-64.
43. Barnes M, Houston D, Worsnop CJ, et al. A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. Am J Respir Crit Care Med 2002;165:773-80.
44. Engleman HM, McDonald JP, Graham D, et al. Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome. Continuous positive airway pressure and mandibular repositioning splint. Am J Respir Crit Care Med 2002;166:855-9.
45. Monasterio C, Vidal S, Duran J, et al. Effectiveness of continuous positive airway pressure in mild sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med 2001;164:939-43.
46. Engleman H, Martin S, Deary I, et al. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. Thorax 1997;52:114-9.
47. Redline S, Adams N, Strauss ME, et al. Improvement of mild sleep disordered breathing with CPAP compared with conservative therapy. Am J Respir Crit Care Med 1998;157:858-65.
48. Engleman H, Kingshott R, Wraith P, et al. Randomized placebo controlled crossover trial of continuous positive airway pressure for mild sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999;159:461-7.
49. Marshall NS, Barnes M, Travier N, et al. Continuous positive airway pressure reduces daytime sleepiness in mild to moderate obstructive sleep apnea: a meta-analysis. Thorax 2006;61:430-4.