EDITORIAL

Clinical presentation of OSAS: Gender Does Matter

Comment on Shepertycky MR et al. Differences Between Men and Women in the Clinical Presentation of Patients Diagnosed with Obstructive Sleep Apnea Syndrome. *SLEEP* 2005;28(3):309-314

Terry Young, PhD; Paul E. Peppard, PhD

Department of Population Health Sciences, University of Wisconsin-Madison, Madison, WI

ATTENTION TO SLEEP APNEA IN WOMEN HAS GREATLY INCREASED SINCE GENERAL POPULATION STUDIES, BEGINNING IN 1993, REVEALED A HIGH PREVALENCE OF this condition in women as well as in men.[1-4] The surprise in finding that sleep apnea was not rare in women underscored the lack of data on sleep apnea in women. Furthermore, while the population studies clearly showed that most cases of obstructive sleep apnea (OSA) were medically unrecognized, the disparity appeared to be greater for women. In contrast to the 8:1 or greater ratio of male to female sleep apnea cases seen in clinic populations, only a 2-3:1 ratio was seen in community samples.[5,6] Thus, studies to identify barriers in the clinical recognition of sleep apnea *specifically* in women, in addition to research on sex differences and similarities aimed at investigating etiology and outcomes of sleep apnea, were clearly needed.

Gender-based health care inequities have been associated with many disorders; sleep apnea is far from being unique in this respect. Clinical under-recognition of cardiovascular disease in women has been a major concern for at least 20 years.[7,8] Resolute pursuit of this issue has produced a great deal of data on sources and consequences of inequity in health care for women with heart disease, as well as on how clinic biases arise in general.[9-13] Failure to understand differences in how heart disease presents and progresses in women compared with men and less aggressive evaluation of women with symptoms were identified as key problems. Are these problems at the root of the clinical under-recognition of sleep apnea in women?

Shepertycky and colleagues have sought to answer part of this question in their study, "Differences between Men and Women in the Clinical Presentation of Patients Diagnosed with Obstructive Sleep Apnea Syndrome," reported in this issue of *Sleep*. In this study of 260 women and men diagnosed with OSA, the investigators pursued the complex issue of possible gender differences in patient characteristics in the context of biases that influence whether a woman with OSA ultimately becomes diagnosed or not. Of the few published studies on gender differences in OSA, this report, coming from a research group that has shown strong commitment to better understanding sleep apnea in women,[1,14] is unique in the wealth of data on presenting complaints, medical and sleep symptoms, medical history, life style exposures, and duration of symptoms. In addition, the study is based on a sample in which men were matched to women on severity defined by the apnea-hypopnea index (AHI) and Epworth Sleepiness Scale (ESS), and on age and BMI. The matching factors are basically considered to be confounding factors: this aspect of the design controls for the often-noted findings that OSA in women may be uniquely manifested by a lower frequency of apnea and hypopnea episodes, perhaps explained by more episodes of upper airway resistance without frank apnea events[15] or a concentration of events in REM, rather than non-REM sleep,[16,17] and less severe sleepiness.[3,6] Consequently, we can assume that the observed gender differences in this report are not simply due to differences in degree of severity or type of OSA in women versus men. But, as with all matching designs, in forcing similarity into the comparison groups, the sample is distorted from the typical clinical patient mix. Thus, in interpreting the results, it must be remembered that clinical characteristics of women and men who *have the same AHI, ESS, BMI, and age* are being compared.

The results showed that although both men and women similarly reported snoring, women were approximately 4 times more likely to report insomnia as a presenting complaint and have a history of depression and hypothyroid disease, leading the authors to suggest that greater awareness of these differences could improve the under-diagnosis of sleep apnea in women. But, perhaps this study provides clues to a more complex story. To dig a little deeper, it is helpful to consider how gender differences in presenting problems affect referral and evaluation. In figure 1 illustrating the path of help-seeking for OSA, the opportunities to miss sleep apnea in women, particularly those without typical symptoms, are many. At the individual level, women who do have typical symptoms may fail to get feedback from bedpartners and thus be unaware of the need to seek care, or, if aware, may feel uncomfortable about seeking help for a "male" problem. At the next level, a clinician who is unaware that OSA is common in women will likely fail to recognize the problem in even the most symptomatic woman. And, with the current dearth of information on women-specific symptoms, women without typical symptoms will also be missed. Even in the presence of typical symptoms, other co-morbidity, such as depression, may deflect attention from possible OSA and result in referral elsewhere. Finally, at the sleep specialty clinic level, it is possible that women with OSA manifested by lower AHI or less sleepiness may fail to be diagnosed. Recent findings of gender differences in polysomnographic indicators of abnormal breathing events,[16] and suggestions that women report sleepiness differently support this possible source of under-diagnosis in women.[18]

Now, consider the women in the Shepertycky et al study, who end up in the final "OSAS diagnosis" box in figure 1. Looking

Disclosure Statement

Dr. Young has participated in speaking engagements supported by Sanofi, the Swedish Medical Center, and Cephalon; and is on the advisory board on insomnia for Pfizer, Inc. Dr. Peppard has indicated no financial conflict of interest.

Address correspondence to: Terry Young, PhD, University of Wisconsin-Madison, 1300 University Avenue, room 1070, Madison, WI 53706-1510; Tel: (608) 263-5832; Fax: (608) 263-8828; E-mail: tbyoung@wisc.edu

back over the care-seeking pathways, can we conclude from the relative excess of depression, insomnia and hypothyroidism seen in these women that clinicians be urged to consider a diagnosis of OSAS in obese women with a history of those conditions? This recommendation seems reasonable, but other plausible explanations for the findings need to be considered. First, the excess prevalence of these conditions may simply reflect their higher prevalence in women in the general population overall. This is likely to be true for depression and hypothyroidism, but, as the authors point out, the excess insomnia in women in this study exceeded what has been reported in general populations. Interestingly, in the population based Wisconsin Sleep Cohort Study, we found that insomnia described as difficulty initiating sleep was more frequent in women, compared with men, *only in those with AHI >5*, but not in those with AHI<5.[5] Another possibility is that these co-morbid conditions serve as catalysts to seek health care and provide an opportunity to address OSA symptoms. In addition, these conditions, instead of diverting attention from the OSA symptoms, may actually have a synergistic effect, and prompt a sleep clinic referral. Either of these diagnosis-enhancing processes, if more salient in women than men, could account for a relative excess of women with those conditions in the tertiary care sample of the Shepertycky et al. study.

Of special note, the authors reported little gender difference in the recall of duration of sleep symptoms. Of the women in this clinic catchment area, those with AHI severity equal to that of men did not experience strikingly longer delays in diagnosis. And, the presence of depression and insomnia in these women obviously did not divert all attention from their OSA symptoms at the primary care level, since they did end up in a sleep specialty clinic. However, these optimistic findings swing our thoughts to an issue that cannot be addressed with the matched sample of this study: what happens to women who have less severe OSA, perhaps with as yet un-identified women-specific symptoms? Guilleminault and colleagues[15] have long sought to bring attention to the significant proportion of women with upper airway resistance syndrome: sleep-disordered breathing without frank apneic events, accompanied by insomnia and tiredness, but not necessarily by snoring. Is it possible that OSAS diagnosis is delayed in women with less severe OSA symptoms due to the

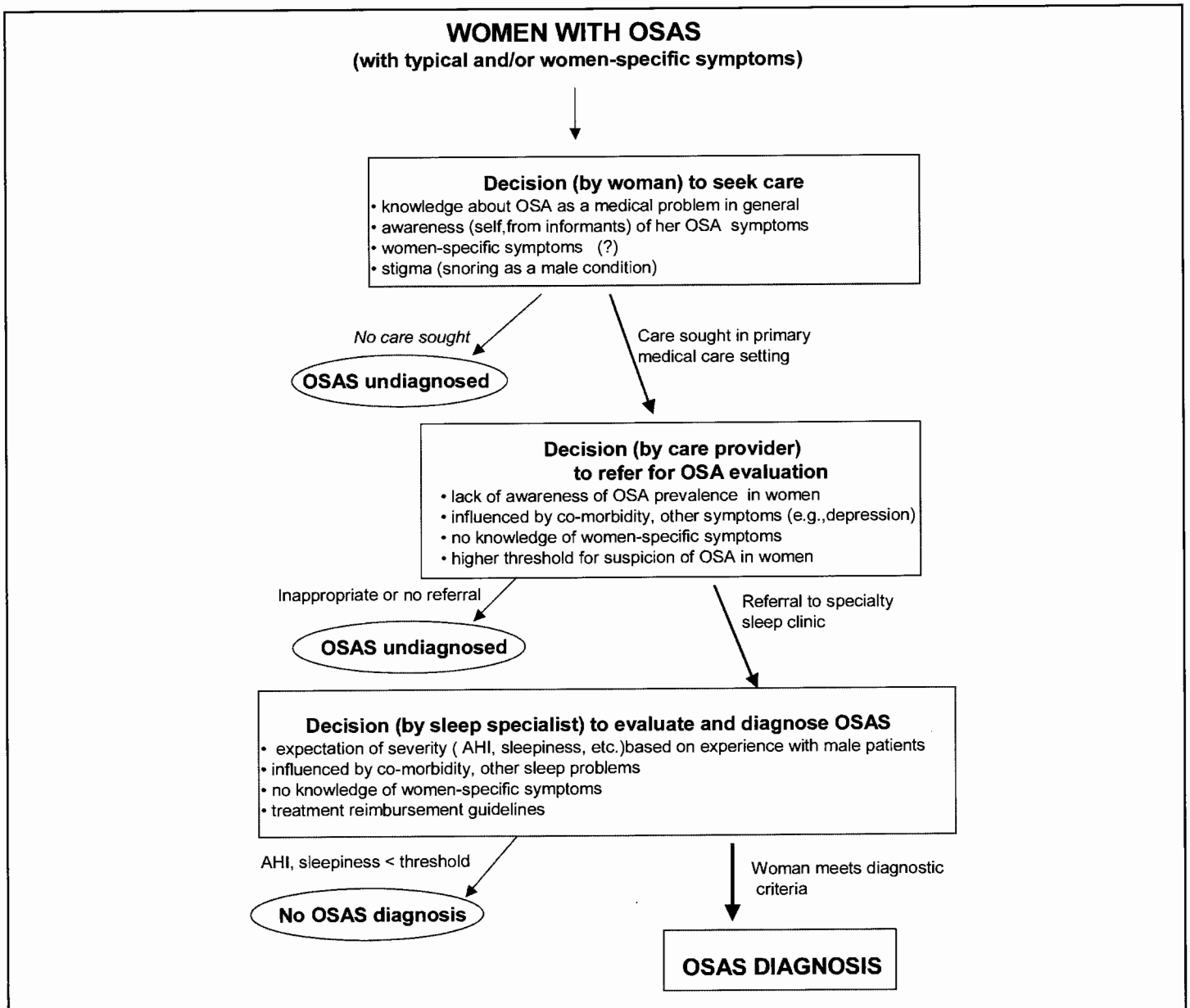

Figure 1—Help-seeking for OSAS in women.

presence of insomnia, depression, hypothyroid disease or other clinical characteristics? Clinicians need to be vigilant against missing or delaying OSAS diagnosis by being "distracted" by those conditions, especially in women where the prevalences of depression and hypothyroidism are overall greater than in men. Those conditions should not be seen as alternative candidates for differential diagnoses in obese women complaining of sleep problems, but as possible markers of OSAS.

Understanding sex and gender influences on health is currently a particularly high profile research agenda.[19] A recent issue of Clinics in Chest Medicine was devoted to sex and gender influences on respiratory disease, including sleep apnea.[20, 21] Looking to the history of gender bias in cardiovascular disease diagnosis, the importance of potential differences in OSA clinical presentation cannot be overstated. A closely related issue is that although women appear to have, on average, less severe OSA according to *diagnostic measures*, the threshold for adverse health outcomes, including mortality associated with sleep apnea may be lower in women.[22, 23] The possibility that women with OSA are missed because they may have a different manifestation of this condition and present with symptoms somewhat different from those of men is often raised, but remains unanswered. The provocative findings from the study of Shepertycky et al. on men and women with severe sleep apnea suggest that women tend to describe their accompanying sleep disturbance as insomnia. While having insomnia did not seem to delay or derail diagnosis for these women, this may not be the case for women with less severe OSA who also complain of insomnia. The Shepertycky et al. findings emphasize the need to identify the manifestations of OSA across the severity spectrum in women and bring this knowledge to bear at the primary care level.

REFERENCES

1. Kapsimalis F, Kryger MH. Gender and obstructive sleep apnea syndrome, part 1: Clinical features. Sleep 2002; 25:412-9.
2. Jordan AS, McEvoy RD. Gender differences in sleep apnea: epidemiology, clinical presentation and pathogenic mechanisms. Sleep Med Rev 2003; 7:377-89.
3. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328:1230-5.
4. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med 2001; 163:608-13.
5. Redline S, Kump K, Tishler PV, Browner I, Ferrette V. Gender differences in sleep disordered breathing in a community-based sample. Am J Respir Crit Care Med 1994; 149:722-6.
6. Young T, Hutton R, Finn L, Badr S, Palta M. The gender bias in sleep apnea diagnosis. Are women missed because they have different symptoms? Arch Intern Med 1996; 156:2445-51.
7. Eaker ED, Chesebro JH, Sacks FM, Wenger NK, Whisnant JP, Winston M. Cardiovascular disease in women. Circulation 1993; 88:1999-2009.
8. Wenger NK, Speroff L, Packard B. Cardiovascular health and disease in women. N Engl J Med 1993; 329:247-56.
9. Mark DB. Sex bias in cardiovascular care: should women be treated more like men? Jama 2000; 283:659-61.
10. Mehilli J, Kastrati A, Dirschinger J, Bollwein H, Neumann FJ, Schomig A. Differences in prognostic factors and outcomes between women and men undergoing coronary artery stenting. JAMA 2000; 284:1799-805.
11. Roger VL, Farkouh ME, Weston SA, et al. Sex differences in evaluation and outcome of unstable angina. Jama 2000; 283:646-52.
12. Roger VL. Cardiovascular disease: an unwomanly disorder? Lancet 2000; 356 Suppl:s10.
13. Pinn VW. Sex and gender factors in medical studies: implications for health and clinical practice. Jama 2003; 289:397-400.
14. Smith R, Ronald J, Delaive K, Walld R, Manfreda J, Kryger MH. What are obstructive sleep apnea patients being treated for prior to this diagnosis? Chest 2002; 121:164-72.
15. Guilleminault C, Stoohs R, Kim YD, Chervin R, Black J, Clerk A. Upper airway sleep-disordered breathing in women. Ann Intern Med 1995; 122:493-501.
16. O'Connor C, Thornley KS, Hanly PJ. Gender differences in the polysomnographic features of obstructive sleep apnea. Am J Respir Crit Care Med 2000; 161:1465-72.
17. Ip MS, Lam B, Tang LC, Lauder IJ, Ip TY, Lam WK. A community study of sleep-disordered breathing in middle-aged Chinese women in Hong Kong: prevalence and gender differences. Chest 2004; 125:127-34.
18. Baldwin CM, Kapur VK, Holberg CJ, Rosen C, Nieto FJ. Associations between gender and measures of daytime somnolence in the Sleep Heart Health Study. Sleep 2004; 27:305-11.
19. Institute of Medicine. Exploring the Biological Contributions to Human Health: Does Sex Matter? Washington: National Academy of Science, 2001.
20. Collop NA, Adkins D, Phillips BA. Gender differences in sleep and sleep-disordered breathing. Clin Chest Med 2004; 25:257-68.
21. Glassberg MK, Murin S, Weisman IM. Sex, gender and resipiratory health and disease. Clin Chest Med 2004; 25:xiii-xiv.
22. Faulx MD, Larkin EK, Hoit BD, Aylor JE, Wright AT, Redline S. Sex influences endothelial function in sleep-disordered breathing. Sleep 2004; 27:1113-20.
23. Young T, Finn L. Epidemiological insights into the public health burden of sleep disordered breathing: sex differences in survival among sleep clinic patients. Thorax 1998; 53 Suppl 3:S16-9.