Published in final edited form as:

Sleep Med. 2008 October ; 9(7): 712–714. doi:10.1016/j.sleep.2008.05.001.

Excessive Daytime Sleepiness in Sleep Apnea: It's Not Just Apnea Hypopnea Index

Alexandros N. Vgontzas, MD^{1,*}

¹ *Sleep Research and Treatment Center, Department of Psychiatry H073, Penn State College of Medicine, 500 University Drive, Hershey, PA 17033*

Excessive daytime sleepiness (EDS) and fatigue (tiredness without increased sleep propensity) are the most common complaints of patients referred to a sleep disorders clinic. In the general population, the prevalence of EDS is estimated to range from 5–20% based on the question asked [1–4]. From published epidemiologic studies, it is clear that there has been a significant increase of sleepiness over the last two decades. For example, Bixler et al. reported a prevalence of 4% of “hypersomnia” in Los Angeles in 1979 [1], whereas moderate to severe EDS was present in about 10% of the general population in central Pennsylvania in 2005 [4]. In the sleep field, it has been assumed that sleep factors, such as sleep fragmentation due to sleep apnea or self-induced sleep restriction, are the major determinants of this “epidemic” of sleepiness and fatigue.

In this issue of *Sleep Medicine*, Roure and his colleagues [5], in a large multicenter cohort of patients with obstructive sleep apnea (OSA) from Spain, examine the role of sleep fragmentation as a result of apnea on EDS. Surprisingly and contrary to the common belief, sleepy patients showed longer sleep duration and increased slow wave sleep compared to the nonsleepy patients with apnea. The authors concluded that sleep apnea and sleep disruption are not the primary determinants of EDS in patients with sleep apnea.

Ten years ago, we published a study indicating that obese patients without sleep apnea are sleepier than nonobese controls using objective daytime sleep tests [6]. Also, in this study and other studies [6,7], morbidly obese patients slept poorly during the night. We were surprised when we found that their daytime sleepiness was not a result of the poor sleep of the preceding night. In fact, analysis showed that those obese patients who were sleepier during the day had higher sleep efficiency at night, whereas those who were less sleepy during the day also had shorter nighttime sleep duration. At that time, we speculated that sleepiness in obese patients most likely reflects metabolic/circadian disturbances. Consequently, and similarly to our study, two more studies showed that in patients with sleep apnea, objective daytime sleepiness is associated with longer nighttime sleep duration [8] or that in obese patients, subjective EDS could not be explained by objective polysomnographic measures of the previous night [9].

Although EDS is considered the cardinal symptom of sleep apnea, their association is rather weak. For example, in clinical practice, frequently patients are examined with a high number of apneas but without significant EDS. This is more common in apneics identified in general

Corresponding Author and Reprint Requests: Alexandros N. Vgontzas, M.D., Penn State University College of Medicine, Department of Psychiatry H073, 500 University Drive, Hershey, PA 17033, Telephone: (717) 531-7278, Fax: (717) 531-6491, Email: avgontzas@psu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

population samples [10–12]. Conversely, patients with a small number of apneas or arousals related to breathing alterations complain of significant EDS not readily explained from the degree of sleep disturbance or any other comorbid conditions. In the Wisconsin cohort of subjects found to have SDB, only 22% of the women and 17% of men reported EDS [10]. In the Penn State cohort, a complaint of EDS was reported by only 17% of those with an apnea hypopnea index (AHI) ≥ 15 [11,12], whereas in the Sleep Heart Health Study, EDS was reported by 16% of those with an AHI > 5 [13]. Also, Bixler and his colleagues in a recent analysis of a large cohort of 1,741 individuals showed that EDS is independently but weakly associated with AHI [4]. In addition, correction of SDB with continuous positive airway pressure (CPAP) does not lead to complete restoration of daytime energy and/or significant improvement of objective measures of sleepiness in many patients [14], and additional administration of stimulants is recommended [15]. These data suggest that sleepiness, in part, is independent of the number of apneas and that other factors may play a significant role.

In subsequent studies we have attempted to explore other possible factors contributing to sleepiness and fatigue. We and others have shown that age, obesity, diabetes, insulin resistance, physical activity, and depression/emotional stress are strong determinants of excessive daytime sleepiness and fatigue in humans [4,16–20], whereas the association of diet-induced obesity and excessive sleep has been demonstrated in animals as well [21]. Furthermore, combining data from clinical and physiological studies, we have suggested that metabolic factors are associated with objective sleepiness, whereas the presence of emotional stress is associated with subjective fatigue but not objective sleepiness [22]. These studies do not refute the role of sleep apnea *per se* or sleep loss in sleepiness; in fact, sleep apnea/sleep disruption is one but not the only or primary determinant of sleepiness in clinical and population samples. The data by Roure et al. [5] strengthen these previous findings and call for further investigation into the possible factors determining EDS and fatigue. From a practical standpoint, there is evidence to support that the evaluation of a sleepy apneic patient should include an assessment of metabolic status, level of exercise, as well as presence of depression or emotional stress. This direction enriches the field of sleep medicine and does not detract from its significance in modern medicine.

The study by Roure et al. [5] does not provide data on patients' metabolic status (e.g., insulin resistance/visceral adiposity), levels of physical activity, or emotional stress. Body mass index does not provide enough information in regard to the metabolic status of their relatively mild obese population. Waist circumference or simple metabolic indices of glycemic control or hyperlipidemia are more accurate indices of the metabolic syndrome and are potentially useful to confirm or reject the importance of metabolic factors in EDS. Also, from this study we cannot exclude the possibility that sleepy apneic patients may suffer from chronic self-induced sleep restriction (which is rather unlikely), that they are more vulnerable to the effects of chronic sleep disruption due to endogenous trait characteristics [23,24], or that their sleepiness is driven partly by genetics [25].

There are many challenges that we need to address in order to understand what makes some apneic patients sleepy and some others not: inconsistencies between subjective vs. objective measures; validity of current instruments; the demarcation of the phenomenology and pathophysiology of objective daytime sleepiness vs. subjective fatigue; detection, definition, and validation of the various subtypes of sleepiness; and, of course, the role of inherited individual predisposition to sleepiness. However, from Roure's study [5] and those preceding their study, there is an important message. In order to understand EDS in clinical and general population samples, we should look beyond the apnea/hypopnea index. If in 1998 these views were "paradoxical" and not "mainstream," in 2008, a stubborn exclusive adherence to AHI (neglecting other factors) in understanding EDS may potentially be harmful to the scientific credibility of the field of sleep medicine.

References

1. Bixler EO, Kales A, Soldatos CR, Kales JD, Healey S. Prevalence of sleep disorders in the Los Angeles metropolitan area. *Am J Psychiatry* 1979;136:1257–1262. [PubMed: 314756]
2. Ohayon MM, Caulet M, Philip P, Guilleminault C, Priest RG. How sleep and mental disorders are related to complaints of daytime sleepiness. *Arch Intern Med* 1997;157:2645–2652. [PubMed: 9531234]
3. Breslau N, Roth T, Rosenthal L, Andreski P. Daytime sleepiness: an epidemiological study of young adults. *Amer J Public Health* 1997;87:1649–1653. [PubMed: 9357347]
4. Bixler EO, Vgontzas AN, Lin HM, Calhoun SL, Vela-Bueno A, Kales A. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol Metab* 2005;90:4510–4515. [PubMed: 15941867]
5. Roure N, Gomez S, Mediano O, Duran J, de la Peña M, Capote F, Teran J, Masa JF, Alonso ML, Corral J, Sánchez-Armengod A, Martinez C, Barceló A, Gozal D, Barbé F. Daytime sleepiness and polysomnography in obstructive sleep apnea patients. *Sleep Med*. 2008
6. Vgontzas AN, Bixler EO, Tan TL, Kantner D, Martin LF, Kales A. Obesity without sleep apnea is associated with daytime sleepiness. *Arch Intern Med* 1998;158:1333–1337. [PubMed: 9645828]
7. Vgontzas AN, Tan TL, Bixler EO, Martin LF, Shubert D, Kales A. Sleep apnea and sleep disruption in obese patients. *Arch Intern Med* 1994;154:1705–11. [PubMed: 8042887]
8. Punjabi NM, O'hearn DJ, Neubauer DN, Nieto FJ, Schwartz AR, Smith PL, Bandeen-Roche K. Modeling hypersomnolence in sleep-disordered breathing. A novel approach using survival analysis. *Amer J Respir Crit Care Med* 1999;159:1703–1709. [PubMed: 10351907]
9. Resta O, Foschino Barbaro MP, Bonfitto P, Giliberti T, Depalo A, Pannacciulli N, De Pergola G. Low sleep quality and daytime sleepiness in obese patients without obstructive sleep apnoea syndrome. *J Intern Med* 2003;253:536–543. [PubMed: 12702031]
10. 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;328:1230–1235. [PubMed: 8464434]
11. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I Prevalence and severity. *Am J Respir Crit Care Med* 1998;157:144–148. [PubMed: 9445292]
12. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, Kales A. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med* 2001;163:608–613. [PubMed: 11254512]
13. Kapur VK, Baldwin CM, Resnick HE, Gottlieb DJ, Nieto FJ. Sleepiness in patients with moderate to severe sleep-disordered breathing. *Sleep* 2005;28:472–477. [PubMed: 16171292]
14. Chugh, DK.; Dinges, DF. Mechanisms of sleepiness in obstructive sleep apnea. In: Pack, AI., editor. *Sleep apnea: pathogenesis, diagnosis, and treatment*. New York: Marcel Dekker, Inc; 2002. p. 265–286.
15. Pack AI, Black JE, Schwartz JR, Matheson JK. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. *Am J Respir Crit Care Med* 2001;164:1675–1681. [PubMed: 11719309]
16. Resnick HE, Carter EA, Aloia M, Phillips B. Cross-sectional relationship of reported fatigue to obesity, diet, and physical activity: results from the third national health and nutrition examination survey. *J Clin Sleep Med* 2006;2:163–169. [PubMed: 17557490]
17. Theorell-Haglöw J, Lindberg E, Janson C. What are the important risk factors for daytime sleepiness and fatigue in women? *Sleep* 2006;29:751–757. [PubMed: 16796213]
18. Resta O, Foschino-Barbaro MP, Legari G, Talamo S, Bonfitto P, Palumbo A, Minenna A, Giorgino R, De Pergola G. Sleep-related breathing disorders, loud snoring and excessive daytime sleepiness in obese subjects. *Int J Obes Relat Metab Disord* 2001;25:669–675. [PubMed: 11360149]
19. Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. *J Clin Endocrinol Metab* 2001;86:517–520. [PubMed: 11158002]
20. Basta M, Lin HM, Pejovic S, Sarrigiannidis A, Bixler E, Vgontzas AN. Lack of regular exercise, depression, and degree of apnea are predictors of excessive daytime sleepiness in patients with sleep apnea: sex differences. *J Clin Sleep Med* 2008;4:19–25. [PubMed: 18350958]

21. Guan Z, Vgontzas AN, Bixler EO, Fang J. Sleep is increased by weight gain and decreased by weight loss in mice. *Sleep*. in press
22. Vgontzas AN, Bixler EO, Chrousos GP. Obesity-related sleepiness and fatigue: the role of the stress system and cytokines. *Ann N Y Acad Sci* 2006;1083:329–44. [PubMed: 17148748]
23. Leproult R, Colecchia EF, Berardi AM, Stickgold R, Kosslyn SM, Van Cauter E. Individual differences in subjective and objective alertness during sleep deprivation are stable and unrelated. *Am J Physiol Regul Integr Comp Physiol* 2003;284:R280–R290. [PubMed: 12529281]
24. Van Dongen HPA, Baynard MD, Maislin G, Dinges DF. Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep* 2004;27:423–433. [PubMed: 15164894]
25. Gottlieb DJ, O’Conno GT, Wilk JB. Genome-wide association of sleep and circadian phenotypes. *BMC Med Genet* 2007;8:S1–S9. [PubMed: 17903291]