



Original Article

Use of the Clinical Global Impression scale in sleep apnea patients – Results from the ESADA database



Marijke Dieltjens^{a, b}, Johan A. Verbraecken^{a, b}, Jan Hedner^{c, d}, Olivier M. Vanderveken^{a, b}, Paschalis Steiropoulos^e, John A. Kvamme^f, Tarja Saaresranta^g, Ruzena Tkacova^h, Oreste Marroneⁱ, Zoran Dogas^j, Sofia Schiza^k, Ludger Grote^{c, d, *}, on behalf of the ESADA collaborators^{1, 2}

^a Antwerp University Hospital, Belgium

^b Faculty of Medicine and Health Sciences, University of Antwerp, Belgium

^c Department of Sleep Medicine, Sahlgrenska University Hospital, Sweden

^d Sahlgrenska Academy, Gothenburg University, Sweden

^e Sleep Unit, Department of Pneumology, Democritus University of Thrace, Alexandroupolis, Greece

^f Sleep Laboratory and ENT Department, Førde Central Hospital, Førde, Norway

^g Division of Medicine and Department of Pulmonary Diseases, Turku University Hospital and Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Finland

^h Department of Respiratory Medicine and Tuberculosis, Faculty of Medicine, P. J. Safarik University and L. Pasteur University Hospital, Kosice, Slovakia

ⁱ National Research Council, Institute of Biomedicine and Molecular Immunology, Palermo, Italy

^j Sleep Medicine Center, Department of Neurosciences, University of Split School of Medicine, Split, Croatia

^k Sleep Disorders Centre, University Hospital, Crete, Greece

ARTICLE INFO

Article history:

Received 6 July 2018

Received in revised form

16 October 2018

Accepted 18 October 2018

Available online 14 November 2018

Keywords:

Sleep apnea

Diagnosis

Comorbidities

Disease severity

Gender

Age

ABSTRACT

Objective/Background: The Clinical Global Impression scale (CGI) reflects the clinician's assessment of the disease impact on patient's global functioning. We assessed predictors of CGI scale rating in patients with obstructive sleep apnea (OSA).

Patients/Methods: Consecutive patients with suspected OSA (n = 7581) were identified in the European Sleep Apnea Database (ESADA). Anthropometrics, comorbidities, apnea severity obtained by polygraphy or polysomnography, and daytime sleepiness [Epworth Sleepiness Scale (ESS)] were assessed. The CGI 7-point scale was completed at the end of the diagnostic process (CGI-severity, ie, CGI-S) and, in a sub-population, at treatment follow-up (CGI-improvement).

Results: CGI-S was rated mild to moderate in 44% of patients. CGI rating at any given apnea intensity was worse in women than in men (p < 0.01). Patients undergoing polygraphy (n = 5075) were more frequently rated as severely ill compared to those studied with polysomnography (19.0% vs 13.0%, p < 0.001). In patients aged ≤65 years, CGI scoring was generally better than in the elderly despite a similar degree of OSA (eg, 'normal, not ill' 24.2% vs 15.3%, p < 0.01, respectively). Independent predictors of CGI rating included age, BMI, AHI, ESS, cardio-metabolic comorbidities, and diagnosis based on polygraphy. CGI-improvement rating (Beta = −0.406, p < 0.01) was superior to sleep apnea severity or ESS-score (Beta = 0.052 and −0.021, p = 0.154 and 0.538 respectively) at baseline for prediction of good CPAP compliance at follow-up.

Conclusions: CGI rating is confounded by gender, age class and the type of sleep diagnostic method. As OSA phenotypes differ, CGI may contribute as a clinical tool to reflect the significance of clinical disease.

© 2018 Elsevier B.V. All rights reserved.

* Corresponding author. ESADA Office, Gothenburg University, Centre for Sleep and Vigilance Disorders, Medicinaregatan 8B, Box 421, S-405 30 Gothenburg, Sweden.

E-mail address: ludger.grote@lungall.gu.se (L. Grote).

¹ The collaborators are listed in the Appendix section.

² <http://www.esrs.eu/committees-networks/sleep-apnea-network-european-sleep-apnea-database-esada.html>.

1. Introduction

Obstructive sleep apnea (OSA) is a prevalent condition that affects up to 17% of adult women and 34% of adult men [1]. The disorder is characterized by non-restorative sleep, excessive daytime sleepiness, impaired cognitive performance, irritability, depression, reduced quality of life, increased risk of traffic accidents [2,3], and an elevated prevalence of cardiovascular and metabolic comorbidity [4–7].

The severity of OSA is conventionally expressed by the Apnea/Hypopnea Index (AHI) or by the Oxygen Desaturation Index (ODI), defined as the number of apneas and hypopneas or oxygen desaturations of $\geq 3/4\%$ per hour of sleep, respectively [8]. However, this rating system relies only on the objective polysomnography (PSG) or home sleep testing with portable monitoring (PG), without taking subjective symptoms or the presence of known risk factors and comorbidities into account [9,10].

OSA is a heterogeneous disease with different phenotypes [9–11]. According to a recent expert group statement, classification of OSA severity using the AHI alone is inappropriate and the need for improved tools that integrate known risk factors, associated comorbidities and patient's complaints (Fig. 1) is urgent [12].

The Clinical Global Impressions (CGI) scale is a well-established tool applied in the evaluation of mental disorders to rate the overall severity of illness in a particular patient [13]. The CGI score provides the physicians' global impression of disease severity in a patient. The rating takes medical history, psychosocial circumstances, symptoms, behavior, as well as the impact of the symptoms identified by the rater into account [14].

The aim of this study was to introduce the CGI scoring as a diagnostic tool in the work-up of OSA and to evaluate how factors systematically may influence CGI-severity rating in OSA, how treatment decisions are influenced by CGI rating, and how OSA treatment is associated with CGI-change at follow up. To avoid misunderstanding, the CGI severity rating is not a tool to predict AHI. In fact, it is hypothesized that CGI severity rating is influenced by apnea intensity, anthropometrics, symptoms and comorbidities. Furthermore, CGI improvement ratings following PAP treatment are expected to reflect treatment compliance and changes in symptomatology.

2. Material and methods

2.1. The European Sleep Apnea Database (ESADA)

The European Sleep Apnea Database (ESADA) has been described elsewhere in detail [15]. In short, the ESADA is a multi-

centre, prospective patient cohort study that currently involves 30 sleep centres distributed across 20 countries in Europe and Israel [15]. Patients with suspected OSA and aged between 18 and 80 years old are eligible for inclusion in the study [15]. The collected data includes anthropometrics, details of daytime symptoms and health-related lifestyle, such as smoking and alcohol consumption, blood tests, medical history, and concomitant medication. The prevalence of psychiatric comorbidity as well as any cardiovascular disease, including systemic and pulmonary hypertension, ischemic heart diseases, left ventricular hypertrophy, valvular heart disease, transient ischemic attack or stroke, post myocardial infarction status, cardiac failure or other cerebrovascular disease was assessed. Metabolic diseases like diabetes, hyperlipidemia and hyperuricemia are determined. The degree of daytime sleepiness is quantified by means of the Epworth Sleepiness Scale (ESS) [16], whereas the degree of sleep apnea is assessed by sleep polygraphy (PG) or polysomnography (PSG) according to the prevailing clinical routine at each participating sleep centre [17].

The data are entered, stored and reviewed in a central web-based database. The ESADA protocol was approved by the respective research ethics committee at each participating site, and informed consent was obtained from all included patients.

2.2. The Clinical Global Impressions scale

The Clinical Global Impressions (CGI) scale was developed to assess the global disease severity in a particular patient, independent of ratings on questionnaires [13]. The CGI rating requires the clinician to rate the overall disease severity in a particular patient at the time of assessment. The scale consists of two subscales used to rate the global patient's condition either before or during a given therapy: the CGI-Severity (CGI-S) or the CGI-Improvement (CGI-I), respectively [13,18]. The CGI-S used in our study is a 7-point scale ranging from 1 being 'normal, not at all ill' to 7 being 'among the most extremely ill patients' [13,18]. The CGI-I is another 7-point scale assessing the effect of therapy on the overall disease severity, ranging from 1 'very much improved' to 7 'very much worse' with 4 denoting 'no change' [18]. In this analysis, data on CGI scores were limited to assessments made by physicians aware of the results of the sleep study and using all available clinical information to rate the overall OSA condition (Fig. 1).

2.3. Statistics

Descriptive analysis of anthropometrics and sleep data (AHI, ODI) are presented for the different CGI-S classes. Spearman correlation was performed to assess the correlation between the CGI-S

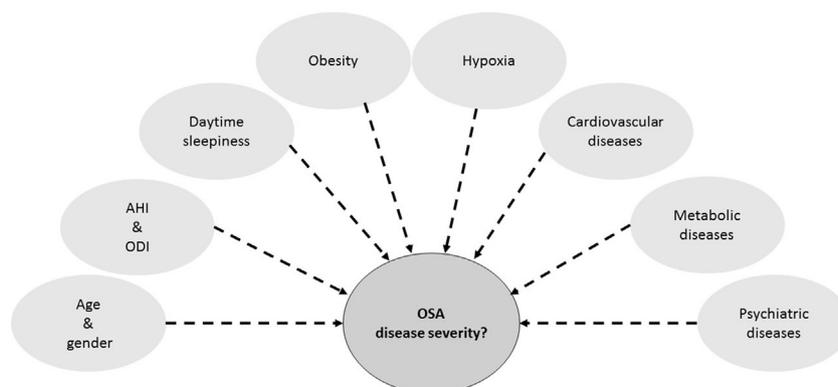


Fig. 1. Variety of factors potentially influencing the CGI classification of OSA disease severity.

rating and established parameters related to OSA severity, such as AHI, ODI, mean and lowest oxygen saturation. Differences in the prevalence of comorbidities were assessed with the Chi square test. CGI-S rating was compared between groups stratified for gender (male vs. female), diagnostic method (PG vs. PSG) and age (cut-off point 65 years) based on established factors to influence OSA severity. An ordinal regression analysis was used to study the independent predictors of the CGI score including age, BMI, AHI, ESS score, and comorbidities as cofactors. In addition, CGI-S and CGI-I ratings were used to predict compliance with PAP treatment using multivariate modeling.

3. Results

3.1. Patient characteristics and Clinical Global Impression scale

The total patient population reviewed in the current study included 18,314 patients from 30 centers. However, the final analysis on the CGI scale was restricted to the eight centers where the CGI rating was performed in a standardized manner, where the sleep physician had completed a comprehensive rating based on the overall clinical information, including OSA related symptoms, physical examination and the sleep test results.

The final analysis cohort included 7581 patients (median age 52.0 years (quartile 1: 43.0; quartile 3: 61.0), mean body mass index (BMI) 30.6 ± 6.8 kg/m², Table 1), and was not significantly different from the total patient population included in the ESADA database.

Approximately one out of four patients (22.8%) of this study population was rated as 'normal' or 'not at all ill' on the CGI rating scale (Table 1). An additional 15.1% of patients were scored as 'borderline ill'. Most of the patients were scored as mildly to moderately ill (44.3%), while 17.8% was scored as markedly ill or even worse. Anthropometric measures and the frequency of comorbidities differed significantly among the seven CGI classes (Table 1, $p < 0.001$ for all parameters).

3.2. Predictors of CGI rating

Age, BMI, AHI, ESS, a cardiovascular diagnosis, metabolic comorbidity and PG as diagnostic method were all independent predictors of a higher CGI score in the ordinal regression analysis (Table 2). Gender and driving exposure did not independently affect the score. Entering ODI or other measures of nocturnal hypoxia instead of AHI did not increase the predictive power of the final model (sensitivity analysis). Psychiatric comorbidity was associated with higher ESS ratings but did not come out as an independent predictor of CGI score. A more detailed description of influences is given below.

3.2.1. OSA disease severity and comorbidities

Conventional measures of OSA disease severity such as AHI and ODI, as well as mean and lowest oxygen saturation all correlated with CGI severity score ($r = 0.528$, $r = 0.534$, $r = -0.426$, $r = -0.325$, all $p < 0.001$, respectively, Table 1). For example, a 'normal' CGI score corresponded to a mean AHI of 10.8 ± 18.2 /h, whereas the most severe CGI score ('among the most extremely ill patients') corresponded to a mean AHI of 76.5 ± 31.1 /h ($p < 0.001$). Furthermore, the CGI score was associated with subjective complaints of daytime sleepiness assessed as the ESS score ($r = 0.186$ and $p < 0.01$). There was a stepwise increase in the prevalence of metabolic and cardiovascular diseases across the CGI scoring classes ($p < 0.001$, respectively, Table 1). The prevalence of comorbid psychiatric disease (based on the physicians' diagnosis) was similar in the CGI scores 'borderline' to 'among the most extremely ill

patients' (between 10.2 and 12.7%) with a lower prevalence in the 'normal' group (6.7%).

3.2.2. Diagnostic method

Home sleep testing with portable monitoring was used in 5075 patients (67.8%) in the total population, while 2411 patients (32.2%) underwent PSG. Patients with PG were more frequently CGI scored as 'normal', or 'not at all ill' compared with the PSG group (25.6% vs. 16.3%), ($p < 0.001$). Moreover, the proportion of patients with a 'markedly ill to extremely ill' CGI score was higher among patients diagnosed with PG (19.9% vs 13.5%), ($p < 0.001$). In addition, within a given CGI category, except for the most extremely ill patients, the AHI was higher if the diagnosis had been made by PSG rather than PG ($p < 0.01$, Fig. 2). In contrast, mean ESS score for each CGI category was consistently higher for the group diagnosed with PG ($p < 0.01$).

3.2.3. Age

Among subjects below the age of 65 years, a higher proportion of patients were scored as 'normal, not ill' compared with patients aged >65 years (24.2% vs. 15.3% respectively, $p < 0.01$). More elderly patients were scored as markedly or severely ill compared with the middle aged individuals (Fig. 3). Within the CGI categories, AHI was comparable between age groups whereas the ESS score was higher in middle-aged compared to elderly OSA patients ($p < 0.01$).

3.2.4. Gender

Although gender did not independently predict CGI score, a number of important gender differences for the CGI Score were observed. The analyzed patient population had a male predominance (5290 (69.8%) males, $p < 0.001$) and among men a slightly higher proportion (40.3%) were scored as 'moderately ill' to 'among the most extremely ill patients' compared to women (32.7%) ($p < 0.01$). This higher CGI rating among men is in line with the higher AHI recorded in male compared to female patients (AHI 26.4 ± 25.3 /h and 16.7 ± 21.5 /h, $p < 0.01$, respectively). We identified a gender related interaction with a lower AHI mean for a given CGI score in women. For example, mean AHI for the CGI score "marked sleep apnea" is 42.6 ± 24.4 events/hour for men compared to 29.9 ± 25.3 in females ($p < 0.01$, Fig. 4). In contrast, women reported a slightly higher degree of daytime sleepiness (ESS score) at any CGI score ($p < 0.01$). The prevalence of comorbidities like metabolic and cardiovascular disease at any CGI level did not differ between genders. However, psychiatric comorbidity was more prevalent in women irrespective of CGI category ($p < 0.01$). Predictors of CGI score in the ordinal regression analysis were different in males and females (Table 2). Cardio-metabolic comorbidities were strong predictors of CGI class in males but not in females. In contrast, BMI was an independent predictor of CGI score in females, not in males.

3.3. CGI scoring and CPAP therapy – treatment indication and longitudinal data

Overall, therapy was prescribed in almost two thirds of all patients (CPAP 50.5%, oral appliances 7%, surgery 4%, active weight reduction 2% and drug treatment in 3%). CPAP prescription rate and CGI rating scores showed a linear relationship whereas the association was non-linear with traditional AHI severity classes (Table 3).

A CGI-Improvement rating was performed in 1455 patients at a first follow-up visit using CPAP therapy (Table 4). Any improvement (minimal to very much improved) was rated in most patients (84.3%) by the sleep expert. CGI-I rating identified only 3.0% of patients where CPAP caused a worsening of symptoms. CPAP

Table 1
Anthropometric data including comorbidities and baseline sleep test results in the seven CGI categories.

	Normal n = 1725 (22.8%)	Borderline n = 1146 (15.1%)	Mildly ill n = 1830 (24.1%)	Moderately ill n = 1530 (20.2%)	Markedly ill n = 885 (11.7%)	Severely ill n = 407 (5.4%)	Among the most extremely ill patients n = 59 (0.8%)	Total group n = 7581	Mann Whitney U-test
Anthropometrics and comorbidities									
Age (years)	47.7 ± 13.5	51.2 ± 12.6 ^a	51.8 ± 12.4 ^a	53.9 ± 11.8 ^{a,b,c}	54.7 ± 12.2 ^{a,b}	55.0 ± 12.2 ^{a,b,c}	54.2 ± 11.6 ^a	51.7 ± 12.8	p < 0.001
BMI (kg/m ²)	28.8 ± 5.3	30.4 ± 7.6 ^a	29.8 ± 5.9 ^{a,b}	30.7 ± 7.3 ^{a,c}	32.6 ± 6.4 ^{a,b,c,d,e}	35.8 ± 7.2 ^{a,b,c,d,e}	40.6 ± 9.4 ^{a,b,c,d,e,f}	30.6 ± 6.8	p < 0.001
Waist circumference (cm)	100.5 ± 14.2	105.6 ± 16.0 ^a	104.6 ± 14.8 ^a	107.2 ± 14.6 ^{a,b,c}	112.6 ± 14.9 ^{a,b,c,d,e}	119.8 ± 15.4 ^{a,b,c,d,e}	130.3 ± 18.1 ^{a,b,c,d,e,f}	106.2 ± 15.8	p < 0.001
Hip circumference (cm)	107.0 ± 10.7	109.5 ± 12.5 ^a	108.8 ± 11.7 ^a	110.0 ± 11.9 ^{a,c}	113.6 ± 13.1 ^{a,b,c,d,e}	117.8 ± 13.0 ^{a,b,c,d,e}	127.2 ± 19.7 ^{a,b,c,d,e,f}	109.9 ± 12.4	p < 0.001
Neck circumference (cm)	39.7 ± 4.5	40.9 ± 5.4 ^a	40.7 ± 4.7 ^a	41.4 ± 4.1 ^{a,b,c}	42.8 ± 4.3 ^{a,b,c,d,e}	44.2 ± 4.2 ^{a,b,c,d,e}	46.0 ± 4.0 ^{a,b,c,d,e,f}	41.1 ± 4.7	p < 0.001
Cardiovascular diseases (%)	29.8	43.4	42.5	48.8	60.1	65.5	76.5	44.5	p < 0.001
Metabolic diseases (%)	18.6	27.6	30.5	33.8	36.8	37.8	42.4	29.3	p < 0.001
Psychiatric diseases (%)	6.7	11.7	10.8	12.7	12.7	11.9	10.2	10.7	p < 0.001
Sleep Apnea Indices									
Apnea/Hypopnea Index (/h)	10.8 ± 18.2	20.1 ± 23.9 ^a	18.1 ± 19.2 ^{a,b}	26.4 ± 20.1 ^{a,b,c}	39.4 ± 25.2 ^{a,b,c,d,e}	57.1 ± 25.0 ^{a,b,c,d,e}	76.5 ± 31.1 ^{a,b,c,d,e,f}	23.5 ± 24.6	p < 0.001
Oxygen Desaturation Index (/h)	7.6 ± 14.0	15.1 ± 21.5 ^a	13.1 ± 17.6 ^{a,b}	19.3 ± 17.6 ^{a,b,c}	33.3 ± 23.5 ^{a,b,c,d,e}	52.7 ± 24.8 ^{a,b,c,d,e}	71.6 ± 31.8 ^{a,b,c,d,e,f}	18.3 ± 22.4	p < 0.001
Mean Oxygen saturation (%)	94.6 ± 1.9	93.8 ± 2.9 ^a	93.9 ± 3.8 ^a	93.4 ± 3.8 ^{a,b,c}	92.4 ± 4.6 ^{a,b,c,d,e}	90.4 ± 3.8 ^{a,b,c,d,e}	85.8 ± 7.3 ^{a,b,c,d,e,f}	93.5 ± 3.7	p < 0.001
Lowest Oxygen Saturation (%)	86.0 ± 7.5	86.0 ± 7.5 ^a	83.1 ± 8.4 ^a	80.8 ± 8.7 ^{a,b,c}	77.0 ± 10.0 ^{a,b,c,d}	70.1 ± 11.9 ^{a,b,c,d,e}	62.7 ± 14.7 ^{a,b,c,d,e,f}	81.7 ± 10.0	p < 0.001
Polysomnographic results in patients studied with polysomnography									
	n = 394	n = 471	n = 672	n = 547	n = 230	n = 84	n = 13	n = 2411	
Apnea/Hypopnea Index (/h)	18.0 ± 23.7	27.6 ± 27.6	24.6 ± 22.7	37.2 ± 21.6	54.5 ± 25.6	62.9 ± 27.9	64.7 ± 45.3	31.3 ± 27.1	p < 0.001
Oxygen Desaturation Index (/h)	11.3 ± 18.4	21.1 ± 26.1	15.8 ± 23.1	21.6 ± 21.8	38.5 ± 27.7	49.0 ± 27.6	46.8 ± 34.3	21.0 ± 25.4	p < 0.001
Sleep Efficiency (%)	84.8 ± 15.8	82.3 ± 15.3	82.0 ± 14.6	82.9 ± 12.0	80.7 ± 13.9	79.0 ± 16.7	80.5 ± 12.1	82.5 ± 14.4	p < 0.001
Sleep stage N1 (%)	10.6 ± 10.5	10.1 ± 9.5	9.7 ± 9.0	11.8 ± 10.7	16.3 ± 14.4	19.3 ± 18.5	16.8 ± 15.1	11.4 ± 11.2	p < 0.001
Sleep stage N2 (%)	58.3 ± 13.9	58.3 ± 13.9	58.6 ± 12.8	53.6 ± 12.3	56.7 ± 14.5	56.0 ± 16.3	56.4 ± 13.7	55.8 ± 13.6	p < 0.001
Sleep stage N3 (%)	15.2 ± 9.1	15.5 ± 8.2	18.8 ± 9.5	16.8 ± 8.8	12.1 ± 8.6	13.6 ± 10.0	14.0 ± 14.0	16.2 ± 9.1	p < 0.001
Sleep stage REM (%)	17.5 ± 10.4	16.8 ± 8.7	18.0 ± 7.9	17.4 ± 7.0	15.2 ± 7.5	12.8 ± 7.6	12.8 ± 6.4	17.0 ± 8.4	p < 0.001

Data are presented as mean ± standard deviation. Mann–Whitney U-test is performed to compare the anthropometric data and baseline polysomnographic parameters between the different CGI categories, with Bonferroni correction. Comorbidity prevalence across CGI classes were analyzed by Chi–Square test.

^a Statistically significant as compared to normal.

^b Statistically significant as compared to borderline.

^c Statistically significant as compared to mildly ill.

^d Statistically significant as compared to moderately ill.

^e Statistically significant as compared to markedly ill.

^f Statistically significant as compared to severely ill.

Table 2
Results of the ordinal regression analysis predicting the CGI scoring set by the sleep physician.

Parameter	Odds ratio	p-value	95% Confidence interval	
Gender	1.122	0.015	1.022; 1.231	
Age	1.017	♂ 1.013 ♀ 1.027	<0.001 ♂ < 0.001 ♀ < 0.001	1.013; 1.021 ♂ 1.008; 1.017 ♀ 1.020; 1.034
Body Mass Index (BMI)	1.010	♂ 0.999 ♀ 1.028	<0.01 ♂ NS ♀ < 0.001	1.003; 1.017 ♂ 0.990; 1.007 ♀ 1.016; 1.040
Apnea/Hypopnea Index (AHI)	1.041	♂ 1.040 ♀ 1.049	<0.001 ♂ < 0.001 ♀ < 0.001	1.039; 1.044 ♂ 1.037; 1.042 ♀ 1.044; 1.054
Epworth Sleepiness Scale (ESS)	1.070	♂ 1.072 ♀ 1.072	<0.001 ♂ < 0.001 ♀ < 0.001	1.061; 1.079 ♂ 1.060; 1.083 ♀ 1.056; 1.089
Presence of cardiovascular comorbidities	1.189	♂ 1.239 ♀ 1.061	<0.05 ♂ < 0.001 ♀ NS	1.079; 1.310 ♂ 1.104; 1.390 ♀ 0.886; 1.271
Presence of metabolic comorbidities	1.136	♂ 1.195 ♀ 1.019	<0.05 ♂ < 0.01 ♀ NS	1.030; 1.253 ♂ 1.064; 1.343 ♀ 0.848; 1.271
Diagnostic method	1.633	♂ 1.711 ♀ 1.452	<0.001 ♂ < 0.001 ♀ < 0.001	1.485; 1.795 ♂ 1.531; 1.912 ♀ 1.210; 1.743

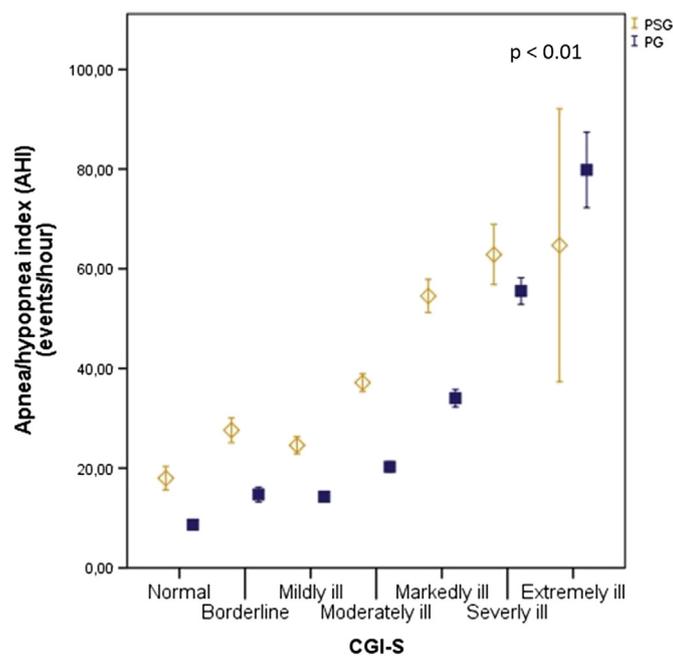


Fig. 2. Mean Apnea Hypopnea Index (y-axis) given for each rating of the CGI-Severity scale at baseline (y-axis). AHI values are given for the two different sleep test diagnostic methods polygraphy (PG, blue) vs polysomnography (PSG, yellow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

compliance differed significantly between CGI rating classes ($p < 0.01$, Table 4) and there was a strong correlation between CPAP use and CGI-I with the highest CPAP use in very much improved patient (Correlation coefficient = -0.412 , $p < 0.01$, Fig. 5). In line with these findings, CGI rating at baseline predicted CPAP compliance in multiple regression analysis. CGI-I rating was a stronger predictor of CPAP compliance (Beta = -0.406 , $p < 0.01$) when compared to AHI or ESS at baseline (Beta = 0.052 and -0.021 , $p = 0.154$ and 0.538 respectively).

4. Discussion

This is, to the best of our knowledge, the first study to apply the CGI scale in a large, unselected clinical cohort of OSA patients referred to academic sleep centres or tertiary level hospitals. Our study has provided five major findings. First, sleep physicians rate OSA severity based mainly on traditional anthropometric data, the

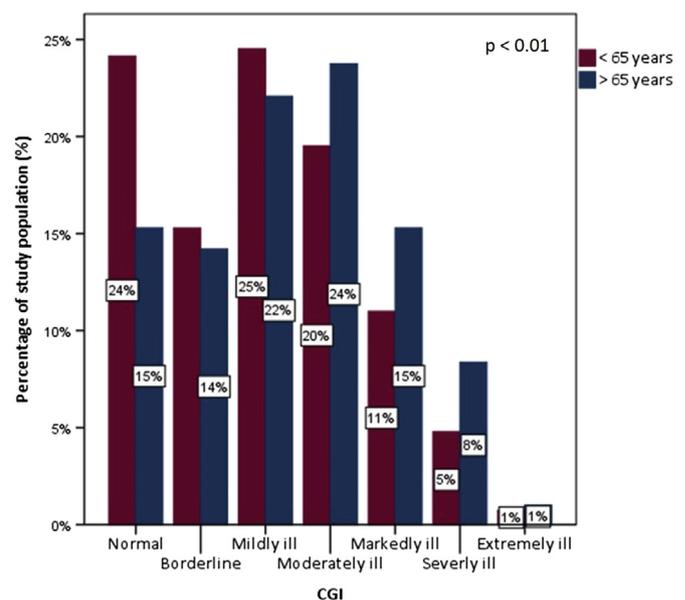


Fig. 3. Bars represent the prevalence (y-axis) of different CGI-Severity rating (x-axis) in the OSA patient population at baseline. Results are shown separately for patients below (red) and above (blue) the age class cut-off of 65 years. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

frequency of respiratory events during sleep, and the degree of daytime sleepiness. The presence of cardiovascular or metabolic comorbidities had a differential impact in the two genders. Second, in the view of the rater, women needed a lower degree of apneic/hypopneic events than men to meet a given CGI severity class. Third, the use of polygraphic sleep recordings as the primary diagnostic method resulted in more “normal cases”, but also in the rather unexpected finding of more severe cases, despite the less sensitive event detection. Fourth, and contrary to recent epidemiological findings suggesting a lower impact of OSA on adverse outcomes in the elderly, OSA disease severity was rated as more severe in this group compared to middle aged patients. Fifth, our findings suggest that the CGI-I scale can be used to monitor the evolution of OSA disease severity over time or under a given therapy. As OSA is expressed in several phenotypes, the CGI may be a complementary tool to better differentiate clinical significance of the disease by not only reflecting conventional sleep study based event frequency indices.

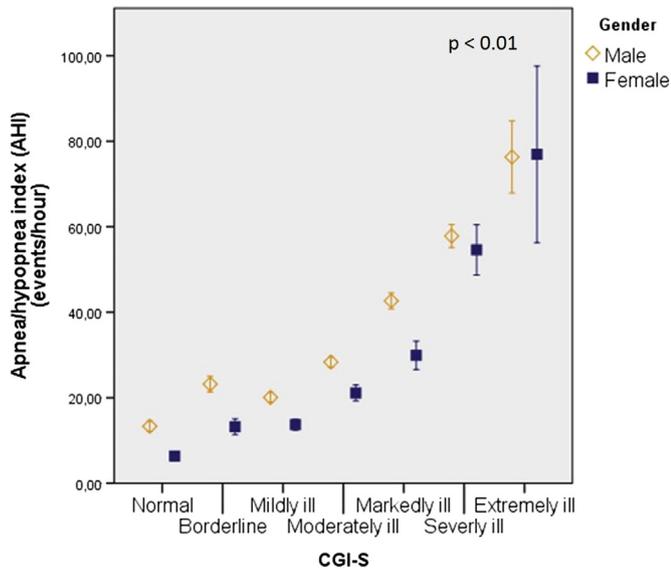


Fig. 4. Mean Apnea Hypopnea Index (y-axis) given for each rating of the CGI-Severity scale at baseline (y-axis). AHI values are given separately for males (yellow) and females (blue). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3

Prescription of continuous positive airway pressure (CPAP) for the different CGI-S subgroups and traditional OSA severity classes.

Normal	92/702 (13.1%)
Borderline	143/430 (31.1%)
Mildly ill	371/836 (44.4%)
Moderately ill	546/688 (79.4%)
Markedly ill	265/302 (87.7%)
Severely ill	148/157 (94.3%)
Among the most extremely ill patients	22/25 (88.0%)
<hr/>	
No OSA (AHI < 5/h)	66/803 (8.2%)
Mild OSA (5 < AHI < 15/h)	212/748 (28.3%)
Moderate OSA (15 < AHI < 30/h)	469/648 (72.4%)
Severe OSA (AHI > 30/h)	788/848 (92.9%)

4.1. Factors influencing the CGI-S score

The CGI scale is a well-established rating tool which originally was applied in psychiatric disorder research to assess the global disease severity [13]. The main current use of the CGI is in clinical drug trials [14]. In our study, the CGI rating was applied as part of the regular diagnostic evaluation of patients with suspected OSA, recruited in the large European Sleep Apnea Database (ESADA). The sample is therefore representative of clinical referrals to European sleep medicine tertiary referral centres.

Approximately one out of four patients with suspected OSA was found to be rated ‘normal’ or ‘not at all ill’. These patients tended to

be younger, less obese with smaller neck, waist and hip circumference, and to have lower AHI and ODI values. This finding is in line with previous studies demonstrating that higher age and overweight are important risk factors for the development of significant OSA [1,19]. Furthermore, a lower AHI and ODI, both classical parameters for the objective diagnosis of OSA, correlated with a lower CGI score. Notably, mean AHI levels for no, borderline or mild sleep apnea did not differ largely which may reflect the ongoing discussion on the clinical significance of mild sleep apnea [20]. Finally, a higher prevalence of known OSA-related co-morbidities was found among patients with a higher CGI score. Taken together, our findings suggest that the process of CGI rating incorporates assessment of several different components and the multivariate analysis identified apneic event frequency, anthropometrics and daytime symptoms as the most important ones.

4.2. Gender analysis

OSA is overrepresented among males [19,21–23] while an atypical clinical presentation has been proposed in females [24]. Hence, women with OSA are more likely to have insomnia, depression and morning headaches. This gender difference appeared to be recognized by the CGI score, which classified 40.3% of men and 32.7% women as moderately to extremely ill. The clinical presentation differed between the sexes and at a similar AHI, the CGI score was lower in men than in women. This finding could in part be explained by the higher ESS value ($p < 0.01$) and the higher degree of psychiatric co-morbidity in women (16% vs 8%, respectively). Unfortunately, we do not have more detailed information on specific symptom burden of depression and/or anxiety as this is usually not assessed in the routine management of sleep apnea in the ESADA centers. It may be speculated that physicians systematically include gender as an important component behind OSA disease severity. Yet, the influence of gender on rating may be more complex, as gender did not constitute an independent predictor of CGI in the final regression model. In line with this, we identified different influences of BMI and cardio-metabolic co-morbidity on CGI score in the gender specific analysis of CGI predictors.

4.3. The impact of diagnostic tests

The ESADA protocol states that any sleep investigation should be performed in accordance with local practice [17]. However, the ESADA protocol mandates that respiratory events are scored using the 2007 American Association of Sleep Medicine (AASM) criteria [15,17,25]. In this study, more patients investigated by a PG method were scored as ‘normal, not at all ill’ compared to patients undergoing PSG. This finding is in line with a previous study of the ESADA cohort demonstrating a substantially higher AHI in patients diagnosed with PSG compared to those investigated with PG [17]. Conversely, the systematic use of PG may result in false negative sleep study results in a significant number

Table 4

Distribution of the Clinical Global Impression-Improvement (CGI-I) rating for patients treated with continuous positive airway pressure (CPAP).

	Number of patients	Percentage of study population	Chi square <math>< 0.01</math>	Compliance with CPAP (h/night) ANOVA $p < 0.01$
Very much improved	522	40.6		5.8 ± 1.5
Much improved	385	29.9		5.2 ± 2.0
Minimally improved	205	15.9		3.8 ± 2.2
No change	152	11.8		2.6 ± 2.4
Any worsening	23	1.8		1.5 ± 1.6
Total	1287	100.0		5.2 ± 2.0

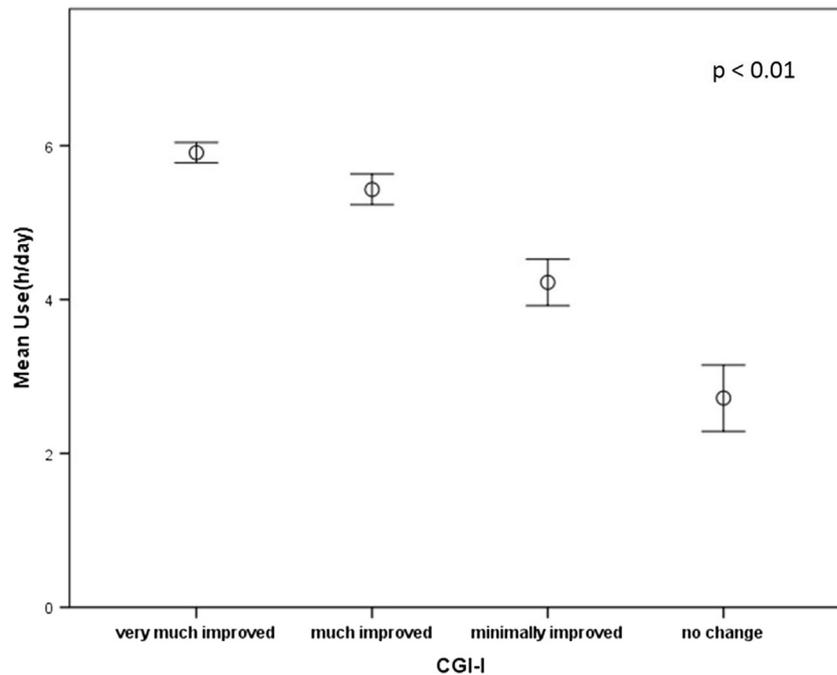


Fig. 5. Mean use of CPAP in hours/night (y-axis) given for the different CGI-Improvement ratings (x-axis).

of patients [12]. In the current study, mean AHI increased linearly within CGI severity categories in patients diagnosed by either PSG or PG. Alternately, those diagnosed with PG more frequently complained of excessive daytime sleepiness and this may explain why they were scored similarly on the CGI scale, despite a lower AHI. In addition, it may be argued that the trained sleep-physician may re-adjust the CGI scoring to the lower sensitivity for AHI detection of the PG method.

4.4. Age related differences

Several studies demonstrated an approximately 2–4-fold higher prevalence of OSA in people aged above 65 years [26–28]. The current study confirmed a higher prevalence of mild to severe OSA in the elderly. However, the AHI was comparable for both age classes among the different CGI classes, and, as expected, younger patients had more severe excessive daytime sleepiness compared to the elderly [29]. Higher CGI scores in older patients may be attributed to the higher prevalence of comorbidities or other active diseases. Conversely, recent studies showed that the impact of OSA on the cardiovascular outcome like blood pressure or disease incidence, is more pronounced in the middle aged population, not in the elderly [30,31].

4.5. Improvement by CPAP treatment

The CGI-Improvement rating was strongly associated with CPAP adherence. Notably, CGI-I rating predicted CPAP compliance better than the AHI or the severity of daytime sleepiness. The relatively poor prognostic value of these conventional OSA severity measures has also been described previously [32–34]. Yet, it is noteworthy that even the CGI severity rating at baseline, an assessment that includes multiple dimensions of disease severity, did not predict CPAP compliance at follow up. Other factors like personality traits or family support may strongly influence CPAP compliance [35] and they are not captured in the routine diagnostic work up in most OSA patients.

4.6. Strengths and limitations

Our study has several strengths, including the, by far, largest sample size of CGI ratings in an OSA patient population. In addition, the study was multi-centric, covering several European countries, and included unselected patients, thereby strongly increase the validity of our findings. Second, our data reflect multiple clinical aspects of OSA, including respiratory event frequency, daytime symptoms, traffic exposure, and important comorbid conditions. Data has also been collected according to a standardized clinical protocol. Study limitations include the fact that there are no universally accepted scoring guidelines for the seven anchor points of the CGI scale. Therefore, the rating requests the clinician to rate the overall disease severity relative to his/her experience [13,18]. In this study, different clinicians were involved in the CGI rating, at least one for each of the eight participating centres. Variable clinical experience may have led to a higher variability in CGI rating. A questionnaire regarding the CGI assessment was sent to all centres in the ESADA study in order to minimize this influence. For the final analysis, we selected only the eight centres that verified rating of the “overall sleep apnea severity”, in a manner that included results from the objective diagnostic method (PSG or PG), the medical history, including regular drug intake, and the subjective symptom evaluation. Furthermore, the CGI rating scale is frequently used in clinical trial protocols, where training of the use of the scale is provided during the study start up process. In the ESADA network, use of the CGI scale was mandated by the study protocol. However, a specific training session was not offered to all physicians involved during the course of such a long term study. Lastly, we did not include CGI data from OSA patients derived from the general population. In fact, we were mostly interested if the CGI can reflect different clinical characteristics within a typical European sleep apnea patient cohort.

4.7. Clinical implication and future research

Although the diagnostic work-up of OSA follows both subjective and objective appraisal, the severity of OSA is conventionally

expressed by the number of respiratory events per hour of sleep [8], without taking the subjective symptoms or both cardiovascular and metabolic comorbidities into account. This practice has recently been challenged [12]. The CGI score, in contrast, provides a method to express the clinician's global impression of the disease and could act as a qualitative instrument to rate the overall impact of OSA on the patients' health status [14]. Our data suggest that factors like gender, age and the diagnostic method used (PG vs. PSG) systematically affect the sleep physician's perception of OSA severity – irrespective of the AHI as the traditional disease severity measure. In fact, the CGI classification may significantly contribute to better patient management. For example, the CGI score may be useful to better predict individuals with the rating “normal, not ill at all” prior to the diagnostic procedure. According to our data, a substantial part of patients may not need a full sleep diagnostic work up. Another area of interest is to further evaluate the potential of the CGI scale to better identify patients with potential non-adherence to CPAP therapy.

The CGI scale should be further validated as a research tool for OSA patients, including inter- or intra-rater variability. Prospective analysis on the evolution of the CGI score under different treatment modalities is another area of research. Furthermore, the appropriateness of current practice in OSA severity scoring, like the observed differences by age and gender, need further evaluation. Finally, the CGI may be helpful in the differentiation of clinical OSA phenotypes and thereby better predict treatment outcome.

5. Conclusion

The CGI rating scale was associated with objective measures of OSA event frequency, daytime symptoms, anthropometric data, as well as with cardiovascular and metabolic comorbidities. Our study identified systematic differences in OSA severity scoring among factors like gender, age, and type of sleep diagnostic test. CGI-Improvement ratings were significantly modified by treatment effects and compliance. The CGI scale may provide a new tool to more broadly assess the various aspects of the clinical burden of OSA.

Funding

The ESADA network has received support from the European Union COST action B26. Unrestricted seeding grants from the ResMed Foundation and the Philips Respironics Foundation for establishment of the organization are gratefully acknowledged. The ESADA network is currently funded as Clinical Research Collaboration by the European Respiratory Society (ERS). Dr. Marijke Dieltjens is the recipient of a ERS Fellowship (STRTF 2015) and holds a Postdoctoral fellowship at Research Foundation—Flanders (FWO)—12H4516N. Olivier Vanderveken holds a Senior Clinical Investigator Fellowship from the Research Foundation—Flanders (FWO)—2016–2021.

Acknowledgement

Excellent technical assistance in terms of centre monitoring and database maintenance was provided by Ann-Christin Lundquist, RN and Lena Engemark, RN. The authors thank the European Sleep Research Society (ESRS) and the ERS for their nonfinancial support in terms of logistics for communication, meetings and data presentations for the ESADA collaborators.

Conflict of interest

Prof. dr. Ludger GROTE has received honorary for lectures from Resmed, Respironics, Astra Zeneca and Itamar. He has received consultancy fees from Weinmann GMBH and Mundipharma Sweden. Prof. dr. Ludger GROTE is coauthor of a pending patent related to sleep apnea treatment.

Prof. dr. Olivier VANDERVEKEN received research support and lecture fees from Inspire Medical Systems and Somnomed, research grant from and consultancy for Philips Respironics, consultancy for Nyxoah and for Galvani, research support from ReVent and from Nightbalance.

Dr. Marijke DIELTJENS, Prof. dr. Johan VERBRAECKEN, Prof. dr. Jan HEDNER, Prof. dr. Paschalis STEIROPOULOS, dr. John KVAMME, Prof. dr. Tarja SAARESANTANA, prof. dr. Ruzena TKACOVA, Prof. dr. Oreste MARRONE, prof. dr. Zoran DOGAS and prof. dr. Sophia SCHIZA do have no conflicts of interests to disclose.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <https://doi.org/10.1016/j.sleep.2018.10.028>.

Appendix. Collaborators in the ESADA project

- Alexandroupolis, Greece
 - Steiropoulos P, Sleep Unit, Department of Pneumology, Democritus University of Thrace, Alexandroupolis, Greece
- Antwerp, Belgium
 - Verbraecken J, Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium
 - Petiet E, Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium
- Athens, Greece
 - Georgia Trakada, Pulmonary Medicine, National and Kapodistrian University of Athens, Athens, Greece
- Barcelona, Spain
 - Montserrat JM, Hospital Clinic i Provincial de Barcelona, Barcelona, IDIBAPS Barcelona and CIBERes, Madrid, Spain
- Berlin, Germany
 - Fietze I, Schlafmedizinisches Zentrum, Charité – Universitätsmedizin Berlin, Germany
 - Penzel T, Schlafmedizinisches Zentrum, Charité – Universitätsmedizin Berlin, Germany
- Brno and Klecany, Czech Republic
 - Ondrej Ludka, Department of Cardiology, University Hospital Brno and International Clinical Research Center, St. Ann's University Hospital, Brno, Czech Republic
- Brussels, Belgium
 - Daniel Rodenstein, Cliniques Universitaires Saint-Luc (Brussels, Belgium)
- Caeceres, Spain
 - Masa JF, Hospital San Pedro de Alcántara, Cáceres, and CIBERes, Madrid, Spain
- Crete, Greece
 - Bouloukaki I. Sleep Disorders Unit, Department of Respiratory Medicine, Medical School, University of Crete, Greece
 - Schiza S, Sleep Disorders Unit, Department of Respiratory Medicine, Medical School, University of Crete, Greece
- Dublin, Ireland
 - Kent B, Guy's and St Thomas' NHS Foundation Trust, Guy's Hospital, London, UK
 - McNicholas WT, Department of Respiratory Medicine, St. Vincent's University Hospital, Dublin, Ireland

- Ryan S, Pulmonary and Sleep Disorders Unit, St. Vincent's University Hospital, Dublin, Ireland
- 11. Edinburgh, United Kingdom
 - Riha RL, Department of Sleep Medicine, Royal Infirmary Edinburgh, Scotland
- 12. Førde, Norway
 - Kvamme JA, Sleep Laboratory, ENT Department, Førde Central Hospital, Førde, Norway
- 13. Giessen, Germany
 - Schulz R, Sleep Disorders Centre, University of Giessen, Lung Centre, Giessen, Germany
- 14. Gothenburg, Sweden
 - Grote L, Sleep Disorders Center, Pulmonary Department, Sahlgrenska University Hospital, and Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Göteborg, Sweden
 - Hedner J, Sleep Disorders Center, Pulmonary Department, Sahlgrenska University Hospital, and Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Göteborg, Sweden
 - Ding Zou, Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Göteborg, Sweden
- 15. Grenoble, France
 - Pépin JL, Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France
 - Levy P, Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France
 - Sebastian Bailly, Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France
- 16. Haifa, Israel
 - Lena Lavie and Peretz Lavie, Centre for Sleep Medicine, Technion Institute of Technology, Haifa, Israel
- 17. Hamburg, Germany
 - Hein H, Sleep Disorders Center, St. Adolf Stift, Reinbeck, Germany
- 18. Izmir, Turkey
 - Basoglu OK, Department of Chest Diseases, Ege University, Izmir, Turkey
 - Tasbakan MS, Department of Chest Diseases, Ege University, Izmir, Turkey
- 19. Klapeida, Lithuania
 - Varoneckas G, Institute Psychophysiology and Rehabilitation, Palanga, Lithuania
- 20. Kosice, Slovakia
 - Joppa P, Department of Respiratory Medicine and Tuberculosis, Faculty of Medicine, P.J. Safarik University and L. Pasteur University Hospital, Kosice, Slovakia
 - Tkacova R, Department of Respiratory Medicine and Tuberculosis, Faculty of Medicine, P.J. Safarik University and L. Pasteur University Hospital, Kosice, Slovakia
- 21. Lisbon, Portugal
 - Staats R, Department of Respiratory Medicine, Hospital de Santa Maria, Lisbon, Portugal
- 22. Lleida, Spain
 - Barbé F, Servei Pneumologia Hospital Arnau de Vilanova and Hospital Santa Maria, Lleida, and CIBERes, Madrid, Spain
- 23. Milano, Italy
 - Lombardi C, Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, St. Luke Hospital, Milan & Department of Medicine and Surgery; University of Milano-Bicocca, Milan, Italy.
- Parati G, Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, St. Luke Hospital, Milan & Department of Medicine and Surgery; University of Milano-Bicocca, Milan, Italy.
- 24. Porto, Portugal
 - Marta Drummond, Pulmonology Department Hospital São João, Medicine Faculty of Porto University, Porto, Portugal
 - Mafalda van Zeller, Pulmonology Department Hospital São João, Medicine Faculty of Porto University, Porto, Portugal
- 25. Palermo, Italy
 - Bonsignore MR, Biomedical Department of Internal and Specialistic Medicine (DiBiMIS), Section of Pneumology, University of Palermo; and CNR Institute of Biomedicine and Molecular Immunology, Palermo, Italy
 - Marrone O, CNR Institute of Biomedicine and Molecular Immunology, Palermo, Italy
- 26. Paris, France
 - Escourrou P, Service d'Explorations Fonctionnelles Multi-disciplinaires Hospital Antoine Beclere, Clamart, France
 - Roisman G, Unité de Médecine du Sommeil, Hopital Antoine-Beclere, Clamart, France
- 27. Prague, Czech Republic
 - Pretl M, Centre for Sleep and Waking Disorders, Department of Neurology, First Faculty of Medicine, Charles University, Prague, and InSpamed, Neurology and Sleep Laboratory, Prague, Czech Republic
- 28. Riga, Latvia
 - Vitols A, Institute of Cardiology, University of Latvia, Riga, Latvia
- 29. Split, Croatia
 - Dogas Z, Sleep Medicine Center, Department of Neuroscience, University of Split School of Medicine, Split, Croatia
 - Galic, T, Sleep Medicine Center, Department of Neuroscience, University of Split School of Medicine, Split, Croatia
- 30. Thessaloniki, Greece
 - Pataka A, Respiratory Failure Unit, G. Papanikolaou Hospital, Thessalonika, Greece
- 31. Turku, Finland
 - Anttalainen U, Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital and Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Finland
 - Saaresranta T, Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital and Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Finland
- 32. Warsaw, Poland
 - Institute of Tuberculosis and Lung Diseases
 - Sliwinski P, 2nd Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
 - Plywaczewski R, 2nd Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
- 33. Medical University of Warsaw
 - Bielicki P, Department of Internal Medicine, Pneumology and Allergology, Medical University of Warsaw, Warsaw, Poland
 - Jan Zielinski, Department of Internal Medicine, Pneumology and Allergology, Warsaw Medical University, Warsaw, Poland

References

- [1] Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013;177(9):1006–14.
- [2] Tkacova R, Dorkova Z. Clinical presentations of OSA in adults. In: Society ER, editor. *European respiratory society Monograph*; 2010. p. 86–103.
- [3] Jennum P, Kjellberg J. Health, social and economical consequences of sleep-disordered breathing: a controlled national study. *Thorax* 2011;66(7):560–6.
- [4] Maeder MT, Strobel W, Christ M, et al. Comprehensive biomarker profiling in patients with obstructive sleep apnea. *Clin Biochem* 2014;48(4–5):340–6.
- [5] Vanderveken OM, Boudewyns A, Ni Q, et al. Cardiovascular implications in the treatment of obstructive sleep apnea. *J Cardiovasc Transl Res* 2011;4(1):53–60.
- [6] Lin CC, Wang HY, Chiu CH, et al. Effect of oral appliance on endothelial function in sleep apnea. *Clin Oral Invest* 2014;19(2):437–44.
- [7] Aurora RN, Punjabi NM. Obstructive sleep apnoea and type 2 diabetes mellitus: a bidirectional association. *Lancet Respir Med* 2013;1(4):329–38.
- [8] Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American academy of sleep medicine. *J Clin Sleep Med* 2012;8(5):597–619.
- [9] Saarestanta T, Hedner J, Bonsignore MR, et al. Clinical phenotypes and comorbidity in european sleep apnoea patients. *PloS One* 2016;11(10). e0163439.
- [10] Ye L, Pien GW, Ratcliffe SJ, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J* 2014;44(6):1600–7.
- [11] Bonsignore MR, Suarez Giron MC, Marrone O, et al. Personalised medicine in sleep respiratory disorders: focus on obstructive sleep apnoea diagnosis and treatment. *Eur Respir Rev* 2017;26(146).
- [12] McNicholas WT, Bassetti CL, Ferini-Strambi L, et al. Challenges in obstructive sleep apnoea. *Lancet Respir Med* 2018;6(3):170–2.
- [13] Guy W. *Clinical global impressions. ECDEU assessment manual for psychopharmacology (Revised)*. Rockville: National Institute of Mental Health; 1976. p. 217–21.
- [14] Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)* 2007;4(7):28–37.
- [15] Hedner J, Grote L, Bonsignore M, et al. The european sleep apnoea database (ESADA): report from 22 european sleep laboratories. *Eur Respir J* 2011;38(3):635–42.
- [16] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14(6):540–5.
- [17] Escourrou P, Grote L, Penzel T, et al. The diagnostic method has a strong influence on classification of obstructive sleep apnea. *J Sleep Res* 2015;24(6):730–8.
- [18] Busner J, Targum SD, Miller DS. The Clinical Global Impressions scale: errors in understanding and use. *Compr Psychiatry* 2009;50(3):257–62.
- [19] Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002;165(9):1217–39.
- [20] McNicholas WT, Bonsignore MR, Levy P, et al. Mild obstructive sleep apnoea: clinical relevance and approaches to management. *Lancet Respir Med* 2016;4(10):826–34.
- [21] Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328(17):1230–5.
- [22] Malhotra A, Huang Y, Fogel RB, et al. The male predisposition to pharyngeal collapse: importance of airway length. *Am J Respir Crit Care Med* 2002;166(10):1388–95.
- [23] Malhotra A, White DP. Obstructive sleep apnoea. *Lancet* 2002;360(9328):237–45.
- [24] Shepertycky MR, Banno K, Kryger MH. Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. *Sleep* 2005;28(3):309–14.
- [25] Iber C, Ancoli-Israel S,AC, Quan SF, et al. *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications*. 1st ed. Westchester: American Academy of Sleep Medicine; 2007.
- [26] Bixler EO, Vgontzas AN, Ten Have T, et al. Effects of age on sleep apnea in men: I. Prevalence and severity. *Am J Respir Crit Care Med* 1998;157(1):144–8.
- [27] Young T, Shahar E, Nieto FJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the sleep heart health study. *Arch Intern Med* 2002;162(8):893–900.
- [28] Duran J, Esnaola S, Rubio R, et al. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med* 2001;163(3 Pt 1):685–9.
- [29] Bixler EO, Vgontzas AN, Lin HM, et al. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol Metab* 2005;90(8):4510–5.
- [30] Haas DC, Foster GL, Nieto FJ, et al. Age-dependent associations between sleep-disordered breathing and hypertension: importance of discriminating between systolic/diastolic hypertension and isolated systolic hypertension in the Sleep Heart Health Study. *Circulation* 2005;111(5):614–21.
- [31] Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010;122(4):352–60.
- [32] Weaver TE, Sawyer AM. Adherence to continuous positive airway pressure treatment for obstructive sleep apnoea: implications for future interventions. *Indian J Med Res* 2010;131:245–58.
- [33] Kribbs NB, Pack AI, Kline LR, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993;147(4):887–95.
- [34] McArdle N, Devereux G, Heidarnajad H, et al. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1999;159(4 Pt 1):1108–14.
- [35] Brostrom A, Stromberg A, Martensson J, et al. Association of Type D personality to perceived side effects and adherence in CPAP-treated patients with OSAS. *J Sleep Res* 2007;16(4):439–47.