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Poul Jennum,<sup>1</sup> JeanPierre Coaquira,<sup>2</sup> Sam Mettam,<sup>3</sup> Tatiana Kharkevitch,<sup>3</sup> Morgan Bron,<sup>4</sup> M. Janelle Cambron-Mellott<sup>5</sup>

<sup>1</sup>University of Copenhagen, Copenhagen, Denmark; <sup>2</sup>Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA; <sup>3</sup>Jazz Pharmaceuticals, Inc., Oxford, UK; <sup>4</sup>Former employee of Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA; <sup>5</sup>Kantar, New York, NY, USA.

## Background

- Excessive daytime sleepiness (EDS) is a cardinal manifestation among many patients with obstructive sleep apnoea (OSA), a sleep disorder marked by recurring episodes of partial or complete collapse of the upper airway during sleep<sup>1</sup>
  - OSA is associated with multiple complications, including systemic hypertension and cardiovascular disease, as well as being a precursor of abnormalities of glucose metabolism<sup>2-4</sup>
- EDS is common among OSA patients prior to treatment<sup>5</sup> and may persist in OSA patients following continuous positive airway pressure or other adequate treatment, referred to as "residual sleepiness"<sup>6</sup>
- Past studies have focused on the burden of OSA but have not evaluated the additional influence of EDS on OSA, especially in a broad European context<sup>7,8</sup>
- EDS has been linked to impaired cognition, falls, motor vehicle accidents, and increased mortality in elderly patients<sup>9-12</sup>

## Objective

- To evaluate the burden of illness of EDS among OSA patients using European survey data to describe differences in health-related quality of life (HRQoL), work productivity, and health care resource utilisation (HCRU)

## Methods

- Data from the 2017 European Union 5 (EU5) National Health and Wellness Survey (N = 62,000) were utilised
  - The survey is a self-administered, internet-based questionnaire for adults (≥18 years of age)
  - Participants are identified using stratified random sampling (by age and gender) in each country
  - The outcomes and instruments captured and analysed here include:
    - The Short Form-12, version 2 (SF-12v2<sup>13</sup>) Health Survey domains and subscales
    - Work Productivity and Activity Impairment (WPAI) questionnaire<sup>14</sup>
    - Epworth Sleepiness Scale (ESS)<sup>15</sup>
    - HCRU (ie, number of health care visits, emergency room [ER] visits, and hospitalisations)
- Groups were defined based on self-reported OSA and EDS status, and patients were excluded if they self-reported a narcolepsy diagnosis
  - Those who self-reported not ever experiencing OSA comprised the non-OSA control group
  - Patients who self-reported both experiencing OSA in the last 12 months as well as a diagnosis for this condition were categorised based on their ESS score
    - OSA patients with an ESS score >10 comprised the OSA with EDS group, while those with an ESS score ≤10 comprised the OSA without EDS group
    - Additionally, those with an ESS score >10 were grouped using severity cutoffs for sleepiness: 11 to 12 (mild EDS), 13 to 15 (moderate EDS), and 16 to 24 (severe EDS)<sup>16</sup>
- A bivariate analysis was performed to examine differences based on OSA and EDS status
- Among the OSA groups, a multivariable analysis using generalised linear models was used to control for potential confounders, which were set to average study population values
  - A trend analysis using a polynomial contrast statement was conducted to evaluate the relationship between categorical EDS and the outcomes of interest
  - Due to no adjustments for multiplicity, the P values presented are nominal

## Results

**Table 1. Patient Demographics by OSA and EDS Status**

	OSA with EDS (n = 661)	OSA without EDS (n = 1,347)	Non-OSA controls (n = 57,445)
Age, years, mean (SD)	57.9 (13.0)	60.3 (12.0)	48.3 (16.6)
CCI, mean (SD)	0.74 (1.19)	0.50 (1.11)	0.18 (0.61)
Male, n (%)	435 (65.8)	970 (72.0)	24,941 (43.4)
Country, n (%)			
France	157 (23.8)	462 (34.3)	13,810 (24.0)
Germany	214 (32.4)	381 (28.3)	13,876 (24.2)
United Kingdom	106 (16.0)	183 (13.6)	14,212 (24.7)
Italy	79 (12.0)	145 (10.8)	9,166 (16.0)
Spain	105 (15.9)	176 (13.1)	6,381 (11.1)
Married/living with partner, n (%)	449 (67.9)	949 (70.5)	34,421 (59.9)
Degree, n (%)	214 (32.4)	493 (36.6)	22,961 (40.0)
Labour force participation, n (%)	261 (39.5)	476 (35.3)	31,717 (55.2)

CCI, Charlson comorbidity index; EDS, excessive daytime sleepiness; OSA, obstructive sleep apnoea; SD, standard deviation.

- Compared to patients in the OSA without EDS group, patients in the OSA with EDS group were, on average, slightly younger (58 years of age) and had a relatively higher Charlson comorbidity index (0.74)
- Among patients in the OSA with EDS group, a large proportion were male (66%) and were located in Germany (32%)

**Table 2. Health Comorbidities by OSA and EDS Status**

	OSA with EDS (n = 661)	OSA without EDS (n = 1,347)	Non-OSA controls (n = 57,445)
<b>Comorbidities, n (%)</b>			
High blood pressure	330 (49.9)	709 (52.6)	10,698 (18.6)
High cholesterol	269 (40.7)	521 (38.7)	9,051 (15.8)
Insomnia	186 (28.1)	270 (20.0)	4,671 (8.1)
Gastroesophageal reflux disease	156 (23.6)	233 (17.3)	4,841 (8.4)
Asthma	136 (20.6)	162 (12.0)	4,813 (8.4)
Other sleep difficulties	112 (16.9)	126 (9.4)	3,387 (5.9)
Restless legs syndrome	89 (13.5)	85 (6.3)	1,037 (1.8)
Angina	80 (12.1)	132 (9.8)	4,037 (7.0)
Atrial fibrillation	46 (7.0)	67 (5.0)	778 (1.4)
Fibromyalgia	40 (6.1)	47 (3.5)	887 (1.5)
Unstable angina	34 (5.1)	35 (2.6)	383 (0.7)
Parkinson's disease	5 (0.8)	4 (0.3)	87 (0.2)
<b>Psychiatric comorbidities, n (%)</b>			
Depression	273 (41.3)	359 (26.7)	8,837 (15.4)
Post-traumatic stress disorder	48 (7.3)	47 (3.5)	940 (1.6)

EDS, excessive daytime sleepiness; OSA, obstructive sleep apnoea.

- Compared to other groups, patients in the OSA with EDS group had a relatively higher prevalence of various comorbidities, including depression (41%), insomnia (28%), gastroesophageal reflux disease (24%), and post-traumatic stress disorder (7%)
- Cardio-metabolic risk factors, such as high cholesterol and high blood pressure, were substantially prevalent in all groups, even among the non-OSA controls

## Limitations

- All data are self-reported
- All data are cross-sectional; therefore, causal inferences cannot be made
- The multivariable models adjusted for the Charlson comorbidity index; however, insomnia and other sleep disorders were not included as covariates

**Table 3. Multivariable Analysis: Quality of Life Outcomes by EDS Status, Controlling for Covariates (N = 2,008)**

Dependent variable	OSA without EDS (reference; n = 1,347)	OSA with mild EDS (ESS 11-12; n = 195)	OSA with moderate EDS (ESS 13-15; n = 228)	OSA with severe EDS (ESS 16-24; n = 238)	P value
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
MCS score	45.6 (45.1, 46.2)	45.0 (43.5, 46.4)	42.4 (41.1, 43.8)	40.8 (39.5, 42.1)	<0.001
Vitality	46.9 (46.4, 47.4)	46.7 (45.3, 48.0)	45.6 (44.4, 46.8)	44.2 (43.0, 45.4)	<0.001
Social functioning	44.5 (44.0, 45.0)	43.4 (42.0, 44.7)	41.0 (39.8, 42.2)	40.0 (38.8, 41.2)	<0.001
Role emotional	42.7 (42.1, 43.3)	41.8 (40.2, 43.4)	39.3 (37.8, 40.8)	37.0 (35.5, 38.4)	<0.001
Mental health	46.6 (46.0, 47.1)	46.3 (45.0, 47.7)	43.7 (42.4, 44.9)	42.1 (40.9, 43.4)	<0.001
PCS score	43.7 (43.2, 44.1)	43.3 (42.1, 44.6)	42.1 (40.9, 43.2)	41.0 (39.9, 42.1)	<0.001
Physical functioning	45.4 (44.9, 45.9)	45.0 (43.7, 46.3)	43.6 (42.4, 44.9)	42.2 (41.0, 43.4)	<0.001
Role physical	43.2 (42.7, 43.6)	42.2 (41.0, 43.5)	40.4 (39.3, 41.6)	39.1 (37.9, 40.2)	<0.001
Bodily pain	43.4 (42.8, 43.9)	43.5 (42.0, 44.9)	41.5 (40.1, 42.8)	39.7 (38.4, 41.0)	<0.001
General health	42.0 (41.5, 42.5)	41.6 (40.4, 42.9)	39.8 (38.6, 40.9)	39.2 (38.0, 40.3)	<0.001

CCI, Charlson comorbidity index; CI, confidence interval; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; MCS, Mental Component Summary; OSA, obstructive sleep apnoea; PCS, Physical Component Summary. Covariates appearing in the quality of life models are fixed at the following values: age = 59.4950; CCI = 0.5777; female = 0.3003; married = 0.6962; income \$20,000 to \$39,999 = 0.3924; income \$40,000 or more = 0.2714; BMI\_25 above = 0.8222; SMOKE\_Former = 0.4562; SMOKE\_Current = 0.2261; drinks alcohol = 0.7689; exercise = 0.4955.

- Higher levels of sleep propensity on the ESS are linearly associated with lower reported HRQoL (SF-12v2) outcomes
- On both the Mental Component Summary (MCS) and the Physical Component Summary (PCS), patients in the OSA with severe EDS group reported lower scores, driven in large part by the social functioning, mental health, and role emotional subscales (MCS) and role physical and bodily pain subscales (PCS)

**Table 4. Multivariable Analysis: WPAI by EDS Status, Adjusting for Covariates**

Dependent variable	OSA without EDS (reference)		OSA with mild EDS (ESS 11-12)		OSA with moderate EDS (ESS 13-15)		OSA with severe EDS (ESS 16-24)		P value			
	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)				
Absenteeism % (n = 690)	444	9.7 (7.7, 12.2)	74	12.0 (6.7, 21.2)	0.512	77	16.3 (9.4, 28.2)	0.091	95	20.6 (12.5, 33.9)	0.008	0.031
Presenteeism % (n = 643)	419	24.5 (22.3, 26.9)	68	25.6 (20.3, 32.4)	0.716	71	34.9 (27.8, 43.8)	0.005	85	38.3 (31.1, 47.1)	<0.001	<0.001
Overall work impairment % (n = 690)	444	30.6 (28.0, 33.5)	74	35.4 (28.4, 44.1)	0.237	77	42.1 (33.9, 52.2)	0.008	95	48.4 (39.8, 58.8)	<0.001	<0.001
Activity impairment % (n = 2,008)	1,347	37.4 (35.9, 39.0)	195	38.0 (34.1, 42.4)	0.775	228	44.8 (40.6, 49.6)	0.001	238	48.4 (43.9, 53.3)	<0.001	<0.001

CCI, Charlson comorbidity index; CI, confidence interval; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnoea; WPAI, Work Productivity and Activity Impairment. Covariates appearing in the absenteeism and overall work impairment models are fixed at the following values: DEAGE = 51.2232; CCIQuan = 0.4870; female = 0.2913; married = 0.7058; income \$20,000 to \$39,999 = 0.3957; income \$40,000 or more = 0.3870; BMI\_25 above = 0.7696; SMOKE\_Former = 0.3667; SMOKE\_Current = 0.3159; drinks alcohol = 0.8072; exercise = 0.5522. Covariates appearing in the presenteeism model are fixed at the following values: DEAGE = 51.1897; CCIQuan = 0.4448; female = 0.2877; married = 0.6998; income \$20,000 to \$39,999 = 0.4075; income \$40,000 or more = 0.3826; BMI\_25 above = 0.7667; SMOKE\_Former = 0.3701; SMOKE\_Current = 0.3095; drinks alcohol = 0.8103; exercise = 0.5583. Covariates appearing in the activity impairment model are fixed at the following values: age = 59.4950; CCI = 0.5777; female = 0.3003; married = 0.6962; income \$20,000 to \$39,999 = 0.3924; income \$40,000 or more = 0.2714; BMI\_25 above = 0.8222; SMOKE\_Former = 0.4562; SMOKE\_Current = 0.2261; drinks alcohol = 0.7689; exercise = 0.4955.

- Compared to the OSA without EDS group, the OSA with moderate EDS group experienced heightened presenteeism, overall work impairment, and activity impairment, while the OSA with severe EDS group experienced relatively higher impairment in all WPAI outcomes, including absenteeism
- The data suggest that presenteeism is driving overall work impairment
- Higher impairment on all 4 measures of the WPAI are associated with increased ESS scores (sleep propensity)

**Table 5. Multivariable Analysis: HCRU (Last 6 Months) by EDS Status, Adjusting for Covariates (N = 2,008)**

Dependent variable	OSA without EDS (reference; n = 1,347)	OSA with mild EDS (ESS 11-12; n = 195)	OSA with moderate EDS (ESS 13-15; n = 228)	OSA with severe EDS (ESS 16-24; n = 238)	P value
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Traditional health care visits	8.0 (7.6, 8.4)	8.3 (7.3, 9.5)	0.604	10.9 (9.7, 12.3)	<0.001
GP visits	2.8 (2.7, 3.0)	2.7 (2.3, 3.1)	0.444	3.7 (3.2, 4.2)	<0.001
Internist visits	0.2 (0.1, 0.2)	0.2 (0.1, 0.3)	0.683	0.4 (0.3, 0.5)	<0.001
Nurse practitioner/physician assistant visits	0.3 (0.2, 0.4)	0.2 (0.1, 0.4)	0.423	0.4 (0.2, 0.9)	0.205
Pulmonologist visits	0.2 (0.2, 0.3)	0.2 (0.2, 0.3)	0.690	0.3 (0.2, 0.4)	0.077
Neurologist visits	0.2 (0.1, 0.2)	0.2 (0.1, 0.3)	0.804	0.3 (0.2, 0.5)	0.012
Psychiatrist visits	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)	0.870	0.4 (0.2, 0.6)	0.039
ER visits	0.3 (0.2, 0.3)	0.4 (0.3, 0.5)	0.062	0.3 (0.3, 0.5)	0.103
Hospitalisations	0.3 (0.2, 0.3)	0.3 (0.2, 0.4)	0.823	0.2 (0.2, 0.4)	0.727

CCI, Charlson comorbidity index; CI, confidence interval; EDS, excessive daytime sleepiness; ER, emergency room; ESS, Epworth Sleepiness Scale; GP, general practitioner; HCRU, health care resource utilisation; OSA, obstructive sleep apnoea. Covariates appearing in the HCRU models are fixed at the following values: age = 59.4950; CCI = 0.5777; female = 0.3003; married = 0.6962; income \$20,000 to \$39,999 = 0.3924; income \$40,000 or more = 0.2714; BMI\_25 above = 0.8222; SMOKE\_Former = 0.4562; SMOKE\_Current = 0.2261; drinks alcohol = 0.7689; exercise = 0.4955. Poisson distribution was used for number of internist visits and number of psychiatrist visits instead of negative binomial distribution.

- Compared to OSA patients without EDS, OSA patients with moderate or severe EDS had increased HCRU as it pertains to overall number of traditional health care visits, particularly visits to the neurologist
- OSA patients with moderate EDS reported a relative increase in general practitioner (GP), internist, and psychiatrist utilisation compared to OSA patients without EDS
- OSA patients with severe EDS reported increases in the number of ER visits, as well as hospitalisations, relative to OSA patients without EDS
- Linear trends were observed in the number of traditional health care visits, particularly GP, internist, and neurologist visits, when compared by EDS severity

## Conclusions

- OSA patients with increasing levels of EDS severity were less productive in and out of the workplace, scored lower on both the physical and mental components of the SF-12v2, and also showed a linear trend with regard to health-related visits, even after adjusting for potential confounders
  - As sleep propensity increased, functional impairment on both the SF-12v2 MCS and PCS scores, as well as the subscales, also increased
  - All measures of work productivity and activity impairment were linearly associated with severity of EDS
  - HCRU, in terms of the mean number of interactions with health care providers and ER visits, experienced a linear trend with regard to sleep propensity
- From the perspectives of the patient, the health care system, and the employer, these results suggest that patients with OSA and EDS have a higher socioeconomic and humanistic burden of disease compared to patients with OSA but no EDS, contingent on their degree of EDS severity

