

MODERN AND MULTIDIMENSIONAL APPROACH OF SLEEP APNEEA AS A PUBLIC HEALTH PROBLEM

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Abstract

The obstructive sleep apnea syndrome (OSAS) is a highly prevalent disorder, associated with recurring episodes of partial or complete upper airway occlusion during sleep, which results in marked sleep disturbance, excessive daytime sleepiness, irritability and morning headache, among other symptoms. Sleep apnea is strongly associated with impaired neuropsychological function and reduced quality of life and social functioning. Daytime sleepiness leads to an increased risk for traffic and industrial accidents. OSAS is also independently associated with several cardiovascular complications: not only systemic hypertension but also ischaemic heart disease and stroke. Identifying patients „at risk” and treating them is very important, but at the same time it is time consuming and expensive. Nevertheless, treatment with continuous positive airway pressure (CPAP) has been shown to improve symptoms and quality of life, decrease traffic accidents and may have a positive effect on cardiovascular morbidity. That is why the economic aspects of sleep apnea and the current legislation are an important issue to discuss and manage, for both the patients and the society they live in.

Keywords: obstructive sleep apnea, cost/efficiency, economic, legislation.

Introduction

In today's society, sleep disturbances, although considered an inconvenience, are rarely seen as a medical problem, only a small number of patients using specialized medical services in order to diagnose and treat their sleep related problems.

About 10% of healthy people have daytime sleepiness that has a direct negative impact on the behavior of those affected [1].

Excessive daytime sleepiness (EDS) is a matter of public interest when people are involved in potentially dangerous daily activities for themselves and/or others, by decreasing work capacity, productivity, or, more grave, by having work related or road accidents.

The EDS has diverse causes, it can be seen both in healthy individuals, secondary to sleep deprivation or shift work and also in people with sleep related disorders, such as sleep apnea syndrome (SAS), narcolepsy or sedative abuse [1].

SAS is associated with an increased number of consequences on the human body, both behavioral and physical. Behavioral consequences include EDS, decreased cognitive performance, reducing the reaction

rate, disturbance of attention, irritability, while physical consequences are represented primarily by cardiovascular diseases, especially arterial hypertension, all with negative impact on patients quality of life.

International Classification of Sleep Disorders, Second Edition (ICSD II) divided sleep respiratory disorders into three categories:

1. Central sleep apnea syndrome;
2. Obstructive sleep apnea/hypopnea syndrome (OSAHS or OSAS) and
3. Obesity hypoventilation syndrome [2].

OSAS. Definitions, Prevalence, Diagnosis and Treatment

Obstructive sleep apnea is a respiratory disease characterized by recurrent episodes of upper airway obstruction during sleep, leading to a reduction (hypopnea) or pause (apnea) of breathing at the oro-nasal pathways, associated with increased of respiratory efforts, with intermittent arterial oxygen desaturation, increase of arterial and pulmonary blood pressure, with sleep fragmentation and excessive daytime sleepiness.

Apnea is defined as the absence of oro-nasal airflow for a period greater than 10 seconds.

Hypopnea is an event that involves identifying any subtle reduction of the oro-nasal airflow [3].

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According to the Chicago criteria (1999) we consider a hypopnea when one of the following three criteria is met:

1. An severe airflow reduction more than 50%;
2. A moderate airflow reduction less than 50%, accompanied by a decrease in oxygen saturation (more than 3%); or
3. A moderate airflow reduction less than 50%, with an arousal highlighted on the electroencephalogram [4].

According to ICD II hypopnea is a 30% decrease in oro-nasal airflow, compared with baseline, that lasts more than 10 seconds, accompanied by a decrease in oxygen saturation greater than 4% [2].

Obstructive sleep apnea is characterized by the absence of oro-nasal airflow, associated with the presence of thoraco-abdominal respiratory movements.

Central apnea is the absence of oronasal airflow associated with the absence of thoraco-abdominal respiratory movements, by cessation of all muscles involved in breathing nerve-sparing.

Mixed apnea begins as central apnea and ends as obstructive [5].

OSAS severity is based on frequency of apnea and hypopnea episodes per hour of sleep.

An apnea/hypopnea index, AHI, is the number of apnea and hypopnea episodes recorded in one hour of sleep.

Mild OSAS is characterized by an AHI between 5 to 15 events per hour of sleep. Moderate OSAS: AHI from 15 to 30 events per hour of sleep. Severe OSAS AHI >30 events per hour of sleep [3].

Studies have consistently found that symptomatic OSAS occurs in 2–4% of the adult population. Obstruction of the upper airway during sleep, resulting in repetitive breathing pauses accompanied by oxygen desaturation and arousal from sleep, is characteristic of OSAS. This results in diurnal sleepiness leading to cognitive impairment. Sleep-disordered breathing (SDB; snoring and associated apneas) is common and has a higher prevalence up to 24% of the population [5].

OSAS is more common in males than in females, with a ratio of 2:1. OSAS prevalence increases in mid-life, but the existence of OSAS in childhood, adolescence and older age means that there is no simple positive correlation of OSAS with age [6].

The signs, symptoms and consequences of OSAS are a direct result of the derangements that occur due to repetitive collapse of the upper airway: sleep fragmentation, hypoxemia, hypercapnia, marked swings in intrathoracic pressure, and increased sympathetic activity.

Clinically, OSAS is defined by the occurrence of daytime sleepiness, loud snoring, witnessed breathing interruptions, or awakenings due to gasping or choking in the presence of at least 5 obstructive respiratory events (apneas, hypopneas or respiratory effort related arousals)

per hour of sleep.

The presence of 15 or more obstructive respiratory events per hour of sleep, in the absence of sleep related symptoms is also sufficient for the diagnosis of OSAS due to the greater association of this severity of obstruction with important consequences such as increased cardiovascular disease risk [7].

The presence or absence and the severity of OSAS must be determined before initiating treatment in order to identify those patients at risk of developing the complications of sleep apnea, guide selection of appropriate treatment and to provide a baseline to establish the effectiveness of subsequent treatment.

Diagnostic criteria for OSAS are based on clinical signs and symptoms determined during a comprehensive sleep evaluation, which includes a sleep oriented history and physical examination, and findings identified by sleep testing (polysomnography, usually performed in sleep laboratories, and polygraphy, that can be register at home) [7].

Polysomnography (PSG) is routinely indicated for the diagnosis of sleep related breathing disorders, and polygraphy (PG) is use to diagnose OSA when utilized as part of a comprehensive sleep evaluation in patients with a high pretest likelihood of moderate to severe OSAS. Also, PG is not recommended in patients with major comorbidities, including moderate to severe pulmonary disease, neuromuscular disease or congestive heart failure, or those suspected of having a comorbid sleep disorder.

The use of PSG for evaluating OSAS requires recording the following physiological signals: electroencephalogram (EEG), chin electromyogram (EMG), electro-oculogram (EOG), airflow, oxygen saturation, respiratory effort and electrocardiogram (ECG) or heart rate. It may also be use (optional) body position and leg EMG derivations. Is also mandatory the constant presence of a trained individual who can monitor for technical adequacy, patient compliance and relevant patient behavior. Least but not last a fully equipped sleep laboratory is needed as well as a sleep doctor to validate all the data. Depending on the case at least one night, and often two nights of registration might be required, the first to diagnose and the second to start the treatment under strict surveillance.

On the other hand a PG should record, at a minimum, airflow, respiratory effort and oxygen saturation. PG can be done at home, with the specification that an experienced sleep technician or appropriately trained healthcare practitioner must perform the application of PG sensors or directly educate the patient in the correct application of the sensors.

Although the gold standard for OSAS diagnosis is polysomnography, this method is expensive, not available in all hospitals and frequently has long waiting lists. Respiratory polygraphy instead is a cheaper and more accessible test and correlates well with PSG.

Authors have paid much attention to different diagnostic approaches to OSAS [8]. There are two elements that affect the efficiency of diagnosis, the prevalence of OSAS in the studied population and the diagnostic protocol employed. The diagnostic protocols employed and at the same time the diagnostic costs depend on the use of polysomnography and cardiorespiratory polygraphy.

OSAS should be approached as a chronic disease requiring long term and multidisciplinary management. There are medical, behavioral and surgical options for the treatment of OSAS. Adjuvant therapies are used as needed to supplement the primary treatment options. The patient should be an active participant in the decision on treatment type and taught to contribute to the management of his or her own disease. Positive airway pressure (PAP) is the treatment of choice for mild, moderate and severe OSAS, and should be offered as an option to all patients. Alternative therapies may be offered depending on the severity of the OSAS and the patient's anatomy risk factors and preferences should be discussed in detail [9].

Public Health Aspects

It is well known that the cost of PAP differs greatly from one country to another, depending mainly on whether the device is bought or rented.

Strictly speaking, what varies is not cost but charges. The cost is the aggregate value of the resources needed to provide a health or clinical intervention [8]. PAP device prices are similar across Europe. The main charge difference among countries appears because some National Health Services rent the devices, usually at higher charges.

In Romania the prices for the PAP devices vary from 60 to 150 Euros/month, if the patient rents the machine, to up to 3,000 Euros (depending on the PAP type) if the device is bought. And the worst part is that our National Health Services do not recognize OSAS as a life threatening disease, so they do not support even 1% of the diagnosis or the treatment costs. In Spain, for instance, the PAP service to a patient is provided for 622 Euros per year [8].

Efficacy duration has quite an important impact on cost effectiveness ratios. In some European countries there is a 5 year treatment efficacy period. This 5 year time horizon is based on the available empirical evidence on efficacy duration but at the same time means that PAP becomes totally ineffective after that time. This assumption clearly contradicts general clinical practice in sleep units, which maintain the treatment beyond 5 or 10 yrs.

Treatment with continuous positive airway pressure (CPAP) has been shown to improve symptoms and quality of life, decrease traffic accidents and may have a positive effect on cardiovascular morbidity. The effectiveness of this treatment is directly related to compliance. Strict follow-up is required for improvement, principally in the first few months [10].

OSAS comorbidities

Speaking about morbidity and mortality associated with OSAS, we should know that untreated OSAS can contribute to the development or progression of other disorders.

There is strong epidemiological and clinical evidence for a relationship between sleep apnea, central obesity, type 2 diabetes and metabolic syndrome (MS).

The relationship between obesity and the development of the MS in patients with OSAS is complex and poorly understood [11]. Obesity is generally regarded as a risk factor for both OSAS and MS [12]. However, factors other than obesity appear to play a significant role in the development of metabolic disturbances in patients with OSAS [13], including sleep fragmentation and intermittent hypoxia.

OSAS is independently associated with alterations in glucose metabolism and places patients at an increased risk of the development of type 2 diabetes. Recent reports have indicated that many patients with type 2 diabetes have OSAS [12].

Weight reduction through dieting or bariatric surgery is followed by a reduction in AHI and incidence of diabetes, improved glucose control and reductions in hypertriglyceridaemia [14]. Also, CPAP treatment may improve glycemic control [12].

OSAS has now been shown to be a cause for systemic hypertension [15] and there is some evidence suggesting that it can also cause pulmonary hypertension [16]. OSAS is also associated with ischemic heart disease.

Recent studies have shown that OSAS is associated with an increase in all-cause and cardiovascular mortality, complementing existing evidence that OSAS has a causal relationship in the development of cardiovascular disease [17]. The data are strongest for systemic arterial hypertension, with a number of large population-based studies showing an association between OSAS and development of systemic hypertension, independent of confounding factors such as sex, age and obesity [18]. There are also studies supporting an independent association with ischemic heart disease, atrial fibrillation, stroke and heart failure, and long-term follow-up studies of OSAS patients effectively treated with continuous positive airway pressure have shown a significant benefit in reducing cardiovascular mortality and nonfatal cardiovascular events [19].

OSAS leads to neuropsychological impairment that includes deficits in attention, concentration, vigilance, manual dexterity, memory, verbal fluency and executive function [20].

Accidents

Perhaps the most important complication of OSAS, and the one that has the greatest impact from the public health perspective, is driving accidents. More than one-third of patients with OSAS report having had an accident

or near-accident on account of falling asleep while driving [21]. There is also objective evidence of 1.3-12 fold increases in accident rates among those with sleep apnoea, and accident rates in OSAS patients have been found to be 1.3 to seven times higher than those in the general population [22,23].

OSAS patients that have an AHI greater than 10 events per hour of sleep are 6.3 times more predisposed to driving accidents than those with an AHI lower than 10 events per hour of sleep [23].

Also, the risks for road accidents in all medical conditions reported in literature is 1.2 to 2 times higher compared to the general population, while OSAS has the highest risk, with a relative risk of 3.71, being surpassed only by age and sex, the general risk factors for road accidents [24].

Vigilance testing and driving simulators in studies assessing driving performance in patients with OSAS reveal that performance is markedly reduced and the impairment is not limited to periods when patients actually fall asleep but also occurs when they are awake, owing to reduced vigilance [25].

There is also evidence that OSAS patients have a 50% increased risk of workplace accidents [26]. Also, snoring and daytime sleepiness have doubled the risk of accidents at work, compared with subjects who did not have these accusations. It has been shown that there is a higher rate of domestic and occupational accidents in patients with OSAS, compared with general population and a reduction in the rate of these accidents, 12 months after initiation of continuous positive airway pressure treatment [27].

OSAS economics

Although less discussed, the economics (costs) for diagnosis and treatment of OSAS, as well as road accidents or those work related that appear because of excessive daytime sleepiness or secondary to the decrease of threshold of attention or concentration, is something not to neglect. Because of the impact on individual health, some researchers have attempted to estimate the costs attributable to road accidents due to OSAS.

In the United States of America, more than 800,000 drivers were involved in OSAS-related motor-vehicle collisions in the year 2000 [28]. These collisions cost \$15.9 billion and 1,400 lives in the year 2000. In the United States, treating all drivers suffering from OSAS with CPAP would cost \$3.18 billion, save \$11.1 billion in collision costs, and save 980 lives annually. Therefore, with CPAP treatment, most of these collisions, costs, and deaths can be prevented.

In Australia, economic costs of sleep disorders (OSAS, insomnia and restless leg syndrome being the most important) is about 1% of gross domestic product of this country [29].

In Great Britain cost/efficiency report becomes

significant after at least 2 years of CPAP treatment, and the benefits clearly increase from year to year. The researchers included in their study the direct medical costs (including here also the costs for diagnose and treat OSAS), the preventive effect of cardiovascular and cerebrovascular disease treatment and the road related accidents costs [30].

These data show once again the importance of diagnosis and treatment of sleep apnea drivers. Unfortunately, in few countries, the driving test legislation includes references to sleep apnea syndrome.

OSAS Legislation

At the EU level, the common regulation is the Council Directive 91/439/EEC applicable since July 1, 1996 [31]. Its Annex III lists disorders that are not compatible with driving. These disorders involve vision, audition, locomotion, cardiovascular system, diabetes, neurological and mental disorders, alcohol, drugs, renal disorders and transplantation, but there is no mention of sleepiness or sleep apnea.

The last paragraph of the Directive states that "as a general rule, a driving license should not be given or renewed to any candidate or license holder suffering from a disorder (not mentioned above) likely to compromise safety on the road, except if by authorized medical advice" [32].

Although they are obliged to comply with Directive 91/439/EEC, each country has the right to impose rules more or less stringent. There are countries where data about OSAS being a major risk factor for road accidents have prompted medical experts to promote the modification of national rules for obtaining/renewal of driving license, by introducing OSAS in the list of diseases incompatible with the necessary driving vehicles skills or that require further investigation.

A recently published report [33] detailed the case law in 25 European countries. Ten of these countries mentioned OSAS in their Annex III, namely Belgium, Finland, France, Germany, Hungary, Netherlands, Poland, Spain, Sweden and United Kingdom. In most countries, a patient diagnosed with OSAS may not drive a motor vehicle or may drive it only under certain conditions (for example not allowed to drive on highways or at night), as long as he is not treated, restrictions amounting if he follows a specialized treatment. But nothing is said about the treatment duration, compliance, etc. The other 15 countries do not mention OSAS in their national rules for obtaining/renewal of driving license.

Five countries (Belgium, Spain, France, Sweden and the United Kingdom) had specific regulations involving sleep apnea or narcolepsy, in addition to idiopathic hypersomnia or insomnia. In the Netherlands, sleep disorders are included in a category of loss of consciousness other than epilepsy, and comprise narcolepsy as well as sleep apnea. These regulations have been introduced recently between 1994 (the Netherlands)

and 1998 (Belgium and the UK), and very recently updated in one country (France in 2005) [32].

The general rule is that the presence of the disorder contraindicates the acquisition and/or the maintenance of the driving license. In most cases, drivers or candidates are allowed to obtain or to keep their driving license only if they are effectively treated. This applies to general drivers as well as to professional drivers, but generally the regulations are more restrictive for the last ones. In no case is effective treatment clearly defined, but in some countries the duration of effective treatment is specified, ranging from 1-6 months, with the exception of a requirement of 5 years without an "attack" applying to narcolepsy as well as to sleep apnea.

In Belgium, a questionnaire is completed on the initial application for a license. If, at a later date, OSAS is diagnosed, the driver must send their license to the licensing authority, but may get it back when able to provide a medical certificate stating that they are being adequately treated.

In Spain, a psycho-technical examination is performed by a private office accredited by licensing authorities at the first application, then every 10 yrs before the age of 45 yrs, every 5 yrs until the age of 60 yrs, every 3 yrs until an age of 70 yrs, then yearly. The examination includes a test on a driving simulator in addition to sight, hearing and blood pressure testing. A questionnaire on general health includes medication taken and possible sleepiness. If any abnormality is detected, a report to the licensing authorities is made and the candidate is referred to a sleep centre [22].

In Sweden, a medical certificate is mandatory to apply for a driving license and is usually completed by the general practitioner. This must be renewed after the age of 65 yrs for C, D, E license holders, which therefore indicates that the physician decides whether a patient is fit to drive.

In the UK, an initial version of the document restricted the application of the regulation to "sleepiness leading to sudden and disabling event at wheel" but this was later changed to "excessive awake time sleepiness". OSAS is not specifically mentioned, but "sleep disorders" appear in the section on respiratory disorders.

In Finland, it has become mandatory, since the end of 2004, for physicians to declare unfit drivers, including sleepy drivers, to the licensing authorities. The impact of such a measure remains to be evaluated.

In Germany, there is no mention of sleepiness in the law concerning disabilities incompatible with a driving license, but under the general rule that any driver should be fit, recommendations were issued by the Ministry of Traffic stating that sleepy OSAS drivers should not be allowed to drive and specify criteria for adequate treatment for professional drivers.

In Romania, the Official Monitor no. 631 of 10.09.2010 published Order 1162 for the approval of the minimum physical and mental skills necessary for driving

a motor vehicle'', in which the medical conditions that are considered incompatible with vehicle or tram driver are stipulated, but no mention of OSAS is made [34].

There are many more data published over the years on the road legislation, on the presence or absence of OSAS in the list of diseases that limit the obtaining or renewal of driving license, on the interpretation and enforcement of the law in each country, but the obvious is that currently there are no general rules to apply to all European countries regarding OSAS and current legislation.

Conclusions

In conclusion, it is impossible, in view of the vast quantity of literature that has burgeoned in the field of obstructive sleep apnea/hypopnea syndrome, to present an exhaustive overview of all its legal, economic and general aspects. However, the following main messages remain: obstructive sleep apnea/hypopnea syndrome and sleep-disordered breathing are very common, affecting a significant proportion of the population and, when untreated, cause significant increased social, cardiac and cerebrovascular morbidity and mortality; a significant proportion of patients with obstructive sleep apnea/hypopnea syndrome remain undiagnosed and untreated due to inadequate resources for case detection and investigation. There is a need to identify optimal organizational and economic models to identify patients at risk for additional screening and management, especially in "at-risk" populations.

After 20 years of medical and scientific research, the effects of OSAS on road accidents are clear for the sleep medicine community. However, legal and administrative consequences are not only limited to that. Only a few countries have understood the importance of this issue, by entering certain rules and actions to their legislation. Yet, even these countries are still exposed to excessive road traffic accidents due to drivers with OSAS that transit the roads.

Therefore, the need for a common, unique legislation to apply to all European countries, appears to be increasingly necessary, both to protect millions of people that annually are traveling on roads and to reduce costs resulting from road accidents, work related accidents, caused by people suffering from excessive daytime sleepiness and respiratory sleep disturbances.

References

1. Boisteanu D, Mita-Baciu A, Vasiluta R. Medico-legal implications of respiratory disorders during sleep. *Rom J Leg Med*, 2010; 1:37-42.
2. American Academy of Sleep Medicine. International Classification of Sleep disorders - 2nd Ed (ICSD-2). Diagnostic and coding manual, 2005.
3. Yaggi HK, Strohl KP. Adult Obstructive Sleep Apnea/Hypopnea Syndrome: Definitions, Risk Factors and Pathogenesis. *Clin Chest Med*, 2010; 31:179-186.

4. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep*, 1999; 22:667-689.
5. Jennum P, Riha RL. Epidemiology of sleep apnoea/hypopnoea syndrome and sleep-disordered breathing. *Eur Respir J*, 2009; 33:907-914.
6. Jennum P, Sjol A. Self-assessed cognitive function in snorers and sleep apneics. An epidemiological study of 1,504 females and males aged 30–60 years: the Dan-MONICA II Study. *Eur Neurol*, 1994; 34:204-208.
7. Epstein LJ, Kristo D, Strollo PJ, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med*, 2009; 5:263-276.
8. Mar J, Rueda JR, Duran-Cantolla J, Schechter C, Chilcott J. The cost-effectiveness of nCPAP treatment in patients with moderate-to-severe obstructive sleep apnoea. *Eur Respir J*, 2003; 21:515-522.
9. Levy P, Pepin JL, Tamisier R, Launois-Rollinat S. Outcomes of OSA and indications for different therapies. In: McNicholas WT and Bonsignore MR (eds.), *Sleep Apnoea*, *Eur Respir Mon* 2010; 50:225-243.
10. Andreu AL, Chiner E, Sancho-Chust JN, et al. Effect of an ambulatory diagnostic and treatment programme in patients with sleep apnoea. *Eur Respir J*, 2012; 39:305-312.
11. Bonsignore MR, Eckel J. Metabolic aspects of obstructive sleep apnoea syndrome. *Eur Respir Rev*, 2009; 18:113-124.
12. Levy P, Bonsignore MR, Eckel J. Sleep, sleep-disordered breathing and metabolic consequences. *Eur Respir J*, 2009; 34:243-260.
13. Barcelo A, Pierola J, et al. Free fatty acids and the metabolic syndrome in patients with obstructive sleep apnoea. *Eur Respir J*, 2011; 37:1418-1423.
14. Grunstein RR, Stenlof K, Hedner JA, Peltonen M, Karason K, Sjostrom L. Two year reduction in sleep apnea symptoms and associated diabetes incidence after weight loss in severe obesity. *Sleep*, 2007; 30:703-710.
15. McNicholas WT, Bonsignore MR. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur Respir J*, 2007; 29:156-178.
16. Blankfield RP, Hudgel DW, Tapolyai AA, Zyzanski SJ. Bilateral leg edema, obesity, pulmonary hypertension, and obstructive sleep apnea. *Arch Intern Med*, 2000; 160:2357-2362.
17. Marshall NS, Wong KK, Liu PY, Cullen SR, Knudman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. *Sleep*, 2008; 31:1079-1085.
18. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA*, 2000; 283:1829-1836.
19. Garvey JF, Taylor CT, McNicholas WT. Cardiovascular disease in obstructive sleep apnea syndrome: the role of intermittent hypoxia and inflammation. *Eur Respir J*, 2009; 33:1195-1205.
20. Engleman HM, Kingshott RN, Martin SE, Douglas NJ. Cognitive function in the sleep apnea/hypopnea syndrome (SAHS). *Sleep* 2000;23:S102-S108.
21. Engleman HM, Hirst WS, Douglas NJ. Under reporting of sleepiness and driving impairment in patients with sleep apnea/hypopnoea syndrome. *J Sleep Res*, 1997; 6:272-275.
22. McNicholas WT, Krieger J. Public health and medicolegal implications of sleep apnoea. *Eur Respir J*, 2002; 20:1594-1609.
23. Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. *N Engl J Med*, 1999; 340:881-883.
24. Mwenge GB, Rodenstein D. Public health and legal implications of OSA. In: McNicholas WT and Bonsignore MR (eds.), *Sleep Apnoea*, *Eur Respir Mon*, 2010; 50:216-224.
25. George CF, Smiley A. Sleep apnea and automobile crashes. *Sleep* 1999;22:790-795.
26. Lindberg E, Carter N, Gislason T, Janson C. Role of snoring and daytime sleepiness in occupational accidents. *Am J Respir Crit Care Med*, 2001; 164:2031-2035.
27. Krieger J, Meslier N, Lebrun T, et al. Accidents in obstructive sleep apnea patients treated with nasal continuous positive airway pressure - A prospective study. *Chest*, 1997; 112:1561-1566.
28. Sassani A, Findley LJ, Kryger M, Goldlust E, George C, Davidson TM. Reducing motorvehicle collisions, cost, and fatalities by treating obstructive sleep apnea syndrome. *Sleep*, 2004; 27: 453-458.
29. Hillman DR, Murphy AS, Antic R, Pezzullo L. The economic cost of sleep disorders. *Sleep*, 2006; 29:299-305.
30. Guest JF, Helter MT, Morga A, et al. Cost-effectiveness of using continuous positive airway pressure in the treatment of severe obstructive sleep apnoea/hypopnoea syndrome in the UK. *Thorax*, 2008; 63:860-865.
31. Council Directive 91/439/EEC, OJ L 237, 24.8.1991, p. 0001 – 0024, Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31991L0439:EN:HTML>
32. Krieger J. Sleep apnoea and driving: how can this be dealt with? *Eur Respir Rev*, 2007; 16:106:189-195.
33. Alonderis A, Barbe F, Bonsignore M, et al. Cost Action B-26: medico-legal implications of sleep apnea syndrome: driving license regulations in Europe. *Sleep Med*, 2008; 9:362-375.
34. Ordinul 1162/2010, M. Of. 631/2010, Available from: <http://www.vsc.ro/weblog/wp-content/uploads/2010/09/ordin-1162-din-31.08.2010.pdf>