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Sleep disorders, medical conditions, and road accident risk

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ABSTRACT

Sleep disorders and various common acute and chronic medical conditions directly or indirectly affect the quality and quantity of one's sleep or otherwise cause excessive daytime fatigue. This article reviews the potential contribution of several prevalent medical conditions – allergic rhinitis, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis/osteoarthritis – and chronic fatigue syndrome and clinical sleep disorders – insomnia, obstructive sleep apnea, narcolepsy, periodic limb movement of sleep, and restless legs syndrome – to the risk for drowsy-driving road crashes. It also explores the literature on the cost-benefit of preventive interventions, using obstructive sleep apnea as an example. Although numerous investigations have addressed the impact of sleep and medical disorders on quality of life, few have specifically addressed their potential deleterious effect on driving performance and road incidents. Moreover, since past studies have focused on the survivors of driver crashes, they may be biased. Representative population-based prospective multidisciplinary studies are urgently required to clarify the role of the fatigue associated with common ailments and medications on traffic crash risk of both commercial and non-commercial drivers and to comprehensively assess the cost-effectiveness of intervention strategies.

1. Introduction

The field of occupational medicine generally views fatigue as the cumulative effect of one's work parameters, e.g., shift duration, work hours/week, shift start time, mental/physical workload, job monotony, and commute time, as discussed elsewhere in these proceedings (Williamson et al., 2011). However, we feel this perspective is too restrictive, since many other factors can play a contributing or even prominent role. These include demographic variables, as reviewed elsewhere in these proceedings by Di Milia et al. (2011), various acute and chronic medical conditions (sleep disorders and clinical ailments), and certain prescribed and over-the-counter medications as reviewed here. Health status variables are increasingly gaining attention in occupational medicine in terms of the so-called 'work ability' of employees, i.e., one's ability to meet workplace demands (Ilmarinen, 2001; Tuomi et al., 1998). Yet, thus far they have received comparatively little consideration as a source of excessive fatigue and being a risk factor for commercial and non-commercial drowsy-driving incidents. Thus, the focus of this article is to illustrate the potential contribution of several major sleep and medical disorders that are highly prevalent in the driving population on daytime fatigue and drowsy-driving incidents.

2. Sleep disorders, daytime fatigue, and drowsy-driving incidents

2.1. Nighttime sleep and daytime fatigue

The average sleep duration of healthy adults is generally regarded to be ~7 h (Ohayon et al., 2004). However, a 2009 telephone survey conducted by the National Sleep Foundation (NSF) on 1000 persons found the average sleep duration of many American adults is far less. The 2009 NSF survey used a random sample of landline telephone numbers and professional interviewers to poll adult heads of households (≥18 years of age) across the different regions of the USA and achieved a cooperation rate (number of contacted persons completing an interview/number of contacted persons completing and not completing an interview) of 28%. Some 43% of the respondents reported sleep durations <7 h/night on weekdays, with 20% of these reporting <6 h/night (Sleep in America Poll 2009, NSF, www.sleepfoundation.org, accessed November 5, 2009). Moreover, based on self-defined criteria, 24% of the

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respondents stated they obtained a good night's sleep only a few nights/month or less. Respondents who slept ≤6 h/night, compared to ones who reported sleeping ≥8 h/night, were more likely to report: sleep needs not being met (59% versus 4%), attaining good sleep only a few nights/week, (60% versus 7%), being told by a physician they had a sleep disorder (25% versus 9%), and experiencing at least a few nights/week the previous month either the symptoms of insomnia (89% versus 42%), obstructive sleep apnea (14% versus 4%), or restless legs syndrome (33% versus 11%). In addition, the survey found that those respondents who reported sleeping poorly at night were likely to feel tired, perform inefficiently, and drive drowsy during the daytime.

Although sleep surveys can give rise to unreliable data due to methodological issues and low response rate, the results of the NSF 2009 survey are consistent with those of its previously conducted surveys. Moreover, the findings of the 2009 NSF poll, indicating that short-sleep duration and poor night's sleep are linked with increased daytime fatigue and sleepiness, are consistent with the findings of published epidemiology and research studies (e.g., Kripke et al., 2002; Ohayon and Vechierrini, 2005). However, it is worthy of mention that consistently sleeping >9 h/night has been associated with the identical complaints, perhaps secondary to underlying sleep, organic, and/or psychiatric disorders (Ohayon and Vechierrini, 2005). Short-sleep duration/sleep deprivation is common in shift and night workers, and as a consequence they are more likely to be at higher risk for experiencing increased fatigue than daytime workers and the unemployed (Ohayon and Roth, 2001; Ohayon et al., 2002). This was substantiated by the results of an earlier 2008 Sleep in America Poll in which 58% of shiftworkers reported sleeping <6 h/night and admitted to driving drowsy at least once/month the previous year (NSF, www.sleepfoundation.org, accessed February 20, 2009). It is worthy of mention that 28% of respondents to the 2009 NSF survey reported having driven drowsy and/or having nodded-off at least once/month during the previous year, and it was these drivers, in comparison to those who self-reported never or infrequently driving drowsy the previous year, who were more likely to report their sleep needs were not being met (41% versus 24%).

2.2. Sleep disorders, fatigue, and road accident risk: an overview

Sleep disorders are the most common sources of daytime fatigue and sleepiness. Those with obstructive sleep apnea syndrome (OSAS) frequently complain of excessive daytime fatigue and sleepiness because of non-restorative and continuously disrupted sleep (e.g., Young et al., 1993; Stoohs et al., 1995). This is also the situation with other sleep disorders, such as periodic limb movement disorder (PLMD), narcolepsy, and insomnia (Ohayon et al., 1997). Nonetheless, the relationship between fatigue and sleep complaints is complex. Both can be present in various common medical conditions other than classical sleep disorders, and sleep pathologies and excessive fatigue can be negative outcomes of an organic, mental, or sleep disorder.

Excessive daytime fatigue and sleepiness increase the risk of driving crashes. The findings of a 2002 poll in Ontario Canada (Vanlaar et al., 2008) found >58% of the study sample of 750 drivers admitted to occasionally operating a vehicle while fatigued or drowsy. Furthermore, an alarming 14.5% admitted to having fallen asleep while driving the previous year, with 2% having had a falling-asleep driving incident. These results are comparable to the 2008 NSF Sleep in America Poll. During the 12-month span prior to the survey, 32% of the respondents stated they had driven drowsy ≥once/month, and 36% admitted to having had briefly nodded-off while driving, with 2% having had experienced a drowsy-driving accident or near accident (NSF, www.sleepfoundation.org, accessed February 20, 2009).

Epidemiological studies indicate that sleep-related crashes represent up to 20% of all traffic accidents in industrial societies (Horne and Reyner, 1995; Philip et al., 2001; Connor et al., 2002), and driving drowsy (Häkkänen and Summala, 2000, 2001; Connor et al., 2001) has been identified as the major explanation of fatal road crashes (Mitler et al., 1988). The 2002 National Highway Traffic Safety Administration-sponsored survey conducted by the Gallup organization provides further detail on this matter (http://www.nhtsa.gov/people/injury/drowsy driving1/survey, accessed February 14, 2009). It found that 37% (49% male/26% female) of the surveyed drivers had fallen asleep while driving at some time in their life. Age was a factor in that nodding-off while operating a vehicle only involved 18% of young drivers (<21 years of age), perhaps because of their short driving exposure, versus 30% of senior drivers (>64 years of age). Of particular interest is the fact that 44% of the drivers <21 years of age, who were only half as likely to have had a falling-asleep episode during their short driving history, reported experiencing such an episode during the 6-month period before the survey. A rather unexpected finding was that the greatest proportion (>35%) of the recent falling-asleep events occurred between 6 a.m. and 5 p.m., versus 28% between midnight and 6 a.m. and 17% between 5 p.m. and 9 p.m. More drivers are on the road during the day than night; thus, the proportion of falling-asleep accidents when prorated according to clock time is greatest at night (Langlois et al., 1985). However, the occurrence of such a high proportion of falling time of day-asleep crashes during the daytime highlights the overall importance of excessive fatigue and sleepiness in driving incidents, no matter the time of day.

The 24 h pattern in drowsy-driving crashes has been previously explored and described elsewhere (see Mitler et al., 1988; Williamson et al., 2011). However, it is likely the earlier investigations included some proportion of incidents in which alcohol and controlled substances played at least a partial role. Bruno (2004) investigated the time-of-day occurrence of single-vehicle, nodding-off crashes in which the influence of alcohol and controlled substances was excluded based on forensic evidence from blood and breath samples and/or on-site police officer reports. Distinctly different 24 h patterns were evident when categorized by driver age. Young (18–24 years, Fig. 1A) and middle-aged (25–44 years, Fig. 1B) drivers experienced peak number of nodding-off crashes nocturnally, ~2:30–3:30 a.m., while older drivers (≥64 years, Fig. 1D) experienced peak number of such crashes during the day, ~2 p.m. Certainly, these different temporal patterns are indicative of the distinctively different driving patterns of younger versus older drivers. Nonetheless, the finding that nodding-off crashes are most numerous in the afternoon in older drivers highlights the significance of excessive daytime fatigue and sleepiness in these driving incidents. Of interest also is the evidence of a minor afternoon (so-called 'post-lunch') secondary peak in nodding-off crashes of the two young (18–24 and 25–44 years, Fig. 1 A and B) age groups and a much more prominent one in the two older (44–64 and ≥64 years, Fig. 1C and D) age groups. This is consistent with the previous documentation of a bimodal distribution of traffic crashes during the 24 h period (Langlois et al., 1985; Mitler et al., 1988) and the timing of elevated fatigue level as predicted by biomathematical models of sleep and alertness (Mallis et al., 2004; Dawson et al., 2011).

Concern over sleep-related driving crashes has motivated a variety of prevention programs and campaigns. For example, in 1998 the Council of Scientific Affairs of the American Medical Association reported on the contribution of driver sleepiness to highway accidents and recommended changes in the federal hours-of-service regulations for commercial motor vehicle operators (Lyznicki et al., 1998). In 2002, the National Summit to prevent drowsy driving convened by the National Academy of Sciences in Washington DC gave rise in the USA to the 'The National Action Plan to

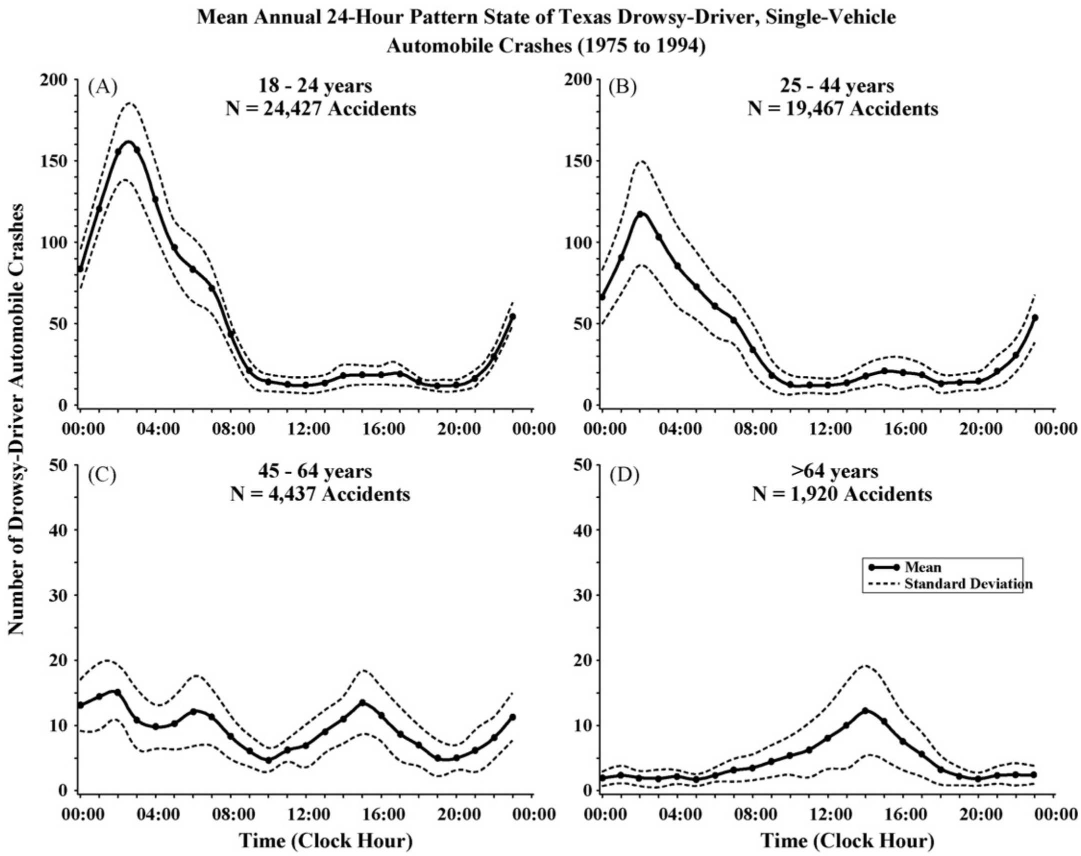

Fig. 1. Mean number (center line) and standard error (upper and lower lines) per clock-hour of nodding-off, single-vehicle (passenger-car) crashes of both male and female drivers combined that occurred yearly between 1975 and 1994 in the State of Texas. Crashes were certified as being due to excessive fatigue or falling asleep based on police and forensic test reports to exclude incidents related to alcohol or controlled substances. The vast majority of the incidents in drivers presumably adhering to a typical lifestyle of daytime activity alternating with nighttime sleep involved those ≤44 years of age. In the two youngest driving groups (18–24 and 25–44 year olds, A and B), the peak number of incidents occurs ∼3 a.m. The secondary afternoon peak between 2 p.m and 5 p.m. in the younger age groups (A and B) is of low prominence. The 24 h pattern is different in the 45–64 and ≥64 year-old driver groups (C and D). In the 45–64 year-old group (C), the early morning peak is attenuated and the afternoon peak prominent, giving rise to a 12 h-like pattern as a group phenomenon. In the ≥64 year-old group (D), there is complete attenuation of the early morning peak with the major peak in the afternoon, ∼2 p.m. Even though there are many-fold more vehicles on the road during the daytime, especially in the morning and late-afternoon/early evening (Langlois et al., 1985), the peak in nodding-off single-vehicle, passenger-car crashes occurs in the middle of the afternoon in older drivers (Bruno, 2004). The scales of the *y*-axis of the two upper (A and B) and bottom (C and D) graphs differ because of difference in the number of nodding-off accidents in the two younger and older age groups. The individual clock-hour values, although discrete data points, are shown as continuous lines to best reveal the specific age-related 24 h patterns.

Prevent Drowsy Driving (www.drowsydriving.org), which involved national, state, and local action initiatives, including research, public policy, and educational programs (Drobnich, 2005). Efforts have been made to improve the regulations regarding driving and sleepiness, and several public campaigns have been developed to sensitize drivers to the risk of drowsy driving ("drive alert-stay alive"). The European Union also has introduced an ambitious program of road safety (European Road Safety Charter, www.erscharter.eu) to halve the number of road deaths by the year 2010.

Although these initiatives are of great importance, we feel they could further benefit from greater involvement of physicians and other healthcare professionals to recognize the signs and symptoms of sleep disorders and detect at risk drivers. Unfortunately, the curriculum of most schools of medicine entails only a rudimentary education of sleep disorders (Bandla et al., 2007; Vigg et al., 2005; Gelir et al., 2004; Papp et al., 2002). As a result, too few primary-care physicians possess an adequate knowledge of sleep medicine. Dentists can also play an important role in detecting at risk drivers by screening their patients for OSAS by presenting oral/maxillary anatomical features and sleep interview (Barsh, 1996; Jauhar et al., 2008). All health professionals are in a position to identify persons with sleep disorders; however, changes to the curriculum of schools of medicine, dentistry, and other health professionals (plus continuing education) will be required to fully capitalize on this potential resource. Moreover, educational and awareness programs, alone, may be of limited value without additional legal and judicial initiatives (Fletcher et al., 2005).

Major problems remain in the identification of those at risk for drowsy driving and the availability of cost-effective means of mitigation. As discussed later in this article, OSAS has been extensively studied as a risk factor for drowsy-driving traffic incidents, as has its treatments as preventive strategies. However, the risk presented by other quite common sleep disorders has received far less attention. The following sections provide an overview of the current understanding of the relationship between sleep disorders, excessive fatigue/tiredness, and drowsy-driving incidents and expose gaps in knowledge that require additional future study.

2.2.1. Insomnia

Insomnia is a subjective perception of one's dissatisfaction with the amount and/or quality of sleep. It may manifest as difficulty in initiating or maintaining sleep or too early awakening and inability to return to sleep (AASM, 1990, 1997; APA, 1994; Ohayon et al., 1997; Ohayon and Reynolds, 2009). It is commonly linked with a decreased quality of life due to complaints of non-restorative sleep, reduced daytime alertness, lethargy, compromised cognitive function, and altered behavioral and/or emotional state. Insomnia may be both a symptom of different ailments, diseases, and stresses and a sleep disorder, itself, when persistent and severe. The symptoms of insomnia can vary in duration, being transient or acute (<3 weeks), short-term/subacute (>3 weeks but <3 months), or long-term/chronic (>3 months). The intensity of the insomnia can also vary from mild or slight (almost nightly), to moderate (occurring nightly with moderate effects on quality of life), and to severe (occurring nightly with moderate impairment of quality of life and rather severe impact on daytime fatigue and mood) (AASM, 1990, 1997).

The 2008 NSF Sleep in America Poll (www.sleepfoundation.org, accessed February 20, 2009) specifically assessed the frequency of sleep disturbance in respondents. It found for at least a few nights each week that: 26% experienced difficulty falling asleep, 42% awoke at an undesired time, and 29% awoke earlier than desired without being able to return to sleep. Based on this single point-in-time telephone survey, an estimated 11% of the respondents could be classified as being at risk for insomnia. However, Ohayon (2008b) through a series of well-designed epidemiology surveys found insomnia to be more prevalent, affecting one-third of the general population of the United States and Europe (Ohayon and Reynolds, 2009) and being responsible for excessive daytime fatigue and sleepiness in 12–15% of adults.

Complaints of insomnia vary among the population. It is two-fold more common in shift and night workers than in day workers and the unemployed (Ohayon and Roth, 2001). Moreover, it seems to be more common among young and middle-aged individuals (Ohayon et al., 1997, 2001, 2002). Disturbed sleep and daytime fatigue are both strong predictors of long-term sickness absence (Åkerstedt et al., 2008; Ohayon and Smirne, 2002; Doi et al., 2003; Ohayon, 2008a). Moreover, daytime fatigue and sleepiness as a consequence of insomnia are of direct safety concern as they can affect accident risk (see Williamson et al., 2011). In this regard, an earlier American Gallup USA poll found that 5% of persons displaying signs of insomnia, compared to 2% of normal sleepers, had been involved in a road crash due to daytime sleepiness (NCSDR, 1993). This corresponds to an odds ratio of 2.5 (Roth and Ancoli-Israel, 1999; Ohayon and Smirne, 2002; Roth and Roehrs, 2003; Walsh, 2004). In a prospective investigation, Léger et al. (2006) studied 369 workers with insomnia (defined according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition) paired with controls, i.e., good sleepers, matched by age, sex, and occupational status. Each participant was interviewed by an occupational physician and answered a self-administered questionnaire relating to work-related criteria. Insomniacs were found to have a higher driving accident rate than controls, and a three-fold greater risk for having two or three serious road crashes.

While these findings substantiate the role of fatigue and sleepiness in drowsy-driving incidents, there remain many unanswered questions. For example, relatively little is known about individual differences in the threshold for and tolerance to fatigue, especially in regard to driving risk. Furthermore, there is little understanding of the exact role that various endogenous and exogenous factors might play in modifying one's threshold for and tolerance to fatigue, as discussed elsewhere in these proceedings (Di Milia et al., 2011).

One way of treating the nighttime sleep complaints of insomnia involves the prescription of hypnotic medications, such as benzodiazepine derivatives, and/or psychoactive therapies when the origin of the insomnia is a mood disorder, such as depression or anxiety (Ohayon and Roth, 2001, 2003). However, these types of medications may substantially impair driving abilities of both young and elderly drivers (Barbone et al., 1998; Leveille et al., 1994). Barbone et al. (1998) examined the association between psychoactive medication use and road-traffic accidents. The number of dispensed prescriptions was used as a measure of exposure in a within-person case-crossover study of drivers ≥18 years of age who had experienced a first road-traffic accident between August 1, 1992 and June 30, 1995 and had used a psychoactive – a benzodiazepine, tricyclic antidepressant, selective serotonin-reuptake inhibitor, or other mainly major tranquillizer – medication up until the date of the accident. A total of 19,386 drivers were involved in a first road-traffic accident during the study period, and 1,731 (9%) were users of one of the study medications. On the day of the road crash, 235 drivers had taken a benzodiazepine (within-patient exposure odds ratio [OR] for an accident 1.62 [95% CI: 1.24–2.12]), 189 drivers had taken a tricyclic antidepressant (0.93 [95% CI: 0.72–1.21]), 84 had taken a selective serotonin-reuptake inhibitor (0.85 [95% CI: 0.55–1.33]), and 47 had taken another psychoactive medication (0.88 [95% CI: 0.62–1.25]). The increased crash risk was significant for the long-half-life benzodiazepine derivatives used as anxiolytics as well as for the short-half-life non-benzodiazepine hypnotic zopiclone taken to manage insomnia. Leveille et al. (1994) conducted a population-based matched case-control study of older drivers involved in injurious crashes in 1987 and 1988. Use of anti-depressants and opioid analgesics by older drivers was associated with increased risk for injurious motor vehicle collisions. Current users of cyclic anti-depressants, in comparison to non-users, had an adjusted relative risk (RR) of 2.3 [95% CI: 1.1–4.8], and for opioid analgesic users it was 1.8 [95% CI: 1.0–3.4). The findings of these studies illustrate the importance of assessing both prescription and over-the-counter nonprescription medications used in the treatment of insomnia and other medical conditions as sources of excessive daytime fatigue and sleepiness, compromised vigilance, and drowsy-driving crash risk.

2.2.2. Obstructive sleep apnea syndrome (OSAS)

OSAS is probably the most studied pathology with respect to traffic accidents, and there are good reasons why this is the case. The prevalence of OSAS in the general population is between 2% and 4% (Young et al., 1993), although it is estimated to be between 26% and 50%, among professional drivers (Engleman et al., 1997; Stoohs et al., 1994). OSAS results in complaints of severe daytime sleepiness (Young et al., 1993), and most importantly many sufferers report sleep-related crashes or near-miss incidents to their clinicians. Indeed, several studies performed during the past 20 years or so reveal a clear positive relationship between OSAS and traffic accidents (Findley et al., 1988; Aldrich, 1989; Haraldsson et al., 1990; Cassel et al., 1991; American Thoracic Society, 1994; Stoohs et al., 1995; Young et al., 1997b; Teran-Santos et al., 1999; Häkkänen and Summala, 2000; Lloberes et al., 2000; George and Smiley, 1999; Masa et al., 2000; Powell et al., 2002; Philip, 2005; Ellen et al., 2006).

In the late 1980s, Findley et al. (1988) published a study involving a small sample of 29 apneic (non-professional) drivers and 35 controls, showing higher risk for road accidents among the former. In a more sophisticated questionnaire study, Haraldsson et al. (1990) reported that untreated apneics showing OSAS symptoms ($n = 140$) had a higher single-car crash rate than controls without OSAS symptoms ($n = 142$). Seventy-three of the OSAS subjects displayed the complete triad of associated symptoms – heavy snoring, sleep disturbances, and daytime sleepiness, and 53% of these, in comparison to 1% of the controls, reported habitual bouts of sleepiness while driving. Although the ratio of drivers who had been involved in one or more multiple-car crashes was similar, the ratio of single-car crashes was seven-fold higher for the OSAS drivers who showed the complete triad of symptoms compared to controls ($p < 0.001$). When corrected for miles driven, the total number of single-car crashes was almost 12-times greater among OSAS drivers who habitually experienced sleep spells than controls ($p < 0.001$).

The reference study on OSAS and driving crashes, however, is considered to be the case-control investigation of Teran-Santos et al. (1999). For the first time, a well-designed protocol compared apneics with controls to evaluate the additional accident risk related to this nocturnal breathing disorder. The patient cases were 102 drivers who received emergency treatment at hospitals following highway crashes, and the controls were 152 patients randomly selected from primary-care centers matched with cases by age and sex. Compared to the controls, apneics having an apnea-hypopnea index (AHI) ≥10 had an odds ratio of 6.3 (95% CI: 2.40–16.02) for experiencing a traffic crash. This relationship remained significant after adjustment for the potential confounders of alcohol consumption, visual-refraction disorders, body mass index (BMI), years of driving, driver age, traffic accident history, medications causing drowsiness, and sleep schedule. George and Smiley (1999) published complementary results on the relationship between AHI and crashes (documented by municipal motor vehicle accident records) occurring during the five-year span preceding the polysomnography-confirmed diagnosis of OSAS. However, in this study only the most severe patients (AHI ≥30) of a large sample (n = 460) of apneic patients showed a crash risk significantly higher than controls. Differences between the studies regarding the AHI threshold for accident risk could reflect difference in investigative methods, driving exposure, and other unknown and uncontrolled variables, including differences in sleep duration/sleep deprivation of the involved drivers as discussed subsequently.

Many other studies confirm the increased accident risk associated with OSAS in non-commercial drivers. For example, Lloberes et al. (2000) studied the road crash rate of non-commercial drivers (n = 189) during the five-year span previous to the polysomnography-confirmed diagnosis of OSAS in comparison to that of a control group composed of hospital staff-workers (n = 40) matched for age and sex and who denied snoring. The self-reported number of driving-off-road incidents was significantly greater in the OSAS group, and the variables associated with this increased risk were: self-reported sleepiness while driving (OR = 5, 95% CI: 2.3-10.9), having quit driving because of sleepiness (OR = 3, 95% CI: 1.1-8.6), and currently working (OR = 2.8, 95% CI: 1.1–7.7). In another study, Masa et al. (2000) interviewed a large group (n = 4002) of randomly selected drivers to identify the prevalence of habitually driving sleepy (HDS). Some 145 (3.6%, 95% CI: 3.1–4.3%) were identified as HDS, and these, compared to age- and sex-matched controls, reported a significantly higher frequency of auto crashes (OR = 13.3, 95% CI: 4.1–43). HDS cases showed a significantly higher prevalence of respiratory sleep disorders than controls. The adjusted OR was 6.0 (95% CI: 1.1–32) for the total respiratory events index (apneas, hypopneas, and other respiratory-effort related arousals) ≥15; although, there was no linear relationship between the severity of sleep apnea, in terms of the respiratory events index, and traffic incidents. However, the frequency of respiratory sleep disorders was significantly higher (OR = 8.5, 95% CI: 1.2–59) in those having had driving incidents. Thus, even though HDS cases constituted a relatively small group (one of 30 drivers), they, nonetheless, accounted for many-fold more road crashes than did the non-HDS cases.

A number of studies also show OSAS plays an important role in road incidents of professional drivers. Stoohs et al. (1995) performed an integrated analysis of sleep-related breathing disorders and self-reported and company-recorded road crashes of 90 commercial long-haul truck drivers. Some 78% of them had an oxygen desaturation index (ODI) ≥5/h sleep, and 10% had an ODI ≥30/h sleep. Overall, ~20% of drivers presented symptoms indicative of severe sleep disturbances. Professional drivers with sleep-disordered breathing had a two-fold higher crash rate/mile exposure than those without sleep-disordered breathing, although crash frequency was not dependent on the severity of the sleep-related breathing disorder. Häkkänen and Summala (2000) surveyed two separate groups, long- (n = 184) and short- (n = 133) haul professional truck drivers, to determine the presence of OSAS symptoms and incidence of drowsy driving during the previous three months. Over 20% reported dozing-off at least twice, and 17% reported near-miss crashes. Factors indicative of sleep apnea occurred in 4% of the long-haul and ~1.4% of short-haul truck drivers.

An additional source of daytime sleepiness in professional drivers, besides OSAS, is sleep deprivation. For one week, Pack et al. (2006) evaluated the respective role of short-sleep duration and OSAS in commercial drivers using the Epworth Sleepiness Scale (ESS; Johns, 1991), objective sleepiness (reduced sleep latency determined by the multiple sleep latency test [MSLT]), and neurobehavioral functioning (lapses in performance as tracking errors) in a divided-attention driving task. From a group of 1,329 commercial drivers, investigators identified 247 drivers at high and 159 drivers at low risk for OSAS. Increased subjective sleepiness was associated with short sleep duration (<5 h/night), but *not* with the severity of OSAS (AHI ≥30 episodes/h). Moreover, heightened objective sleepiness, elevated number of performance lapses, and compromised lane tracking were linked with short sleep duration. Associations with sleep apnea severity were not as robust and not strictly monotonic. Thus, the effects of severe OSAS, characteristic of 4.7% of the drivers, and of short sleep duration, characteristic of 13.5% of the drivers, were similar with respect to the impact on objective sleepiness. However, the actual significance of these findings is compromised by the absence of sufficient normative data for the assessed variables as well as their predictability of crash risk under real road conditions.

Finally, Ellen et al. (2006) performed a meta-analysis of 40 OSAS studies pertaining to driving crash risk of both non-commercial and commercial drivers. For non-commercial drivers, 23 of the 27 studies, including 18 of the 19 that involved a control group, showed a statistically significant increased driving risk for OSAS, with many of the studies documenting it to be two- to three-times higher than the control group. However, risk was not consistently related to OSAS severity. For commercial drivers, the relationship between OSAS and traffic accidents was not robust, in that only one of the three considered studies found an increased crash rate, and, furthermore, in these three studies the association between OSAS and crashes was weak (OR = 1.3). Overall, a correlation between one's self-recognized fatigue/sleepiness and driving incidents was found in only half of all the reviewed studies. Nonetheless, taken together Ellen et al. (2006) meta-analysis confirms the expected association in non-commercial drivers between OSAS and crash risk. Yet, the authors did not confirm this relationship for commercial drivers. Perhaps differences among the driver samples, for example, sleep-span duration/sleep deprivation (Pack et al., 2006), medication use (Barbone et al., 1998; Howard et al., 2004; Leveille et al., 1994), and/or other unknown influences and factors act to modify or obscure the risk of OSAS in commercial drivers.

Indeed, medications have been shown to play a role in road crashes of professional drivers, including ones having OSAS. Howard et al. (2004) used a questionnaire to assess the relationship between driving incidents and excessive sleepiness, sleep-disordered breathing, and medication consumption in a random sample of Australian commercial drivers (n = 2342 respondents) and an additional group (n = 161) of commercial drivers who had undergone polysomnography. Some 24% of the drivers displayed excessive sleepiness. The results of the objective sleep assessments revealed that 59.6% of the drivers had mild to severe sleep-disordered breathing and 15.8% had OSAS. The sleepiest 5% of the commercial drivers, in terms of their ESS scores, showed a ~1.9-fold increased risk for traffic accidents. However, use of narcotic analgesic and antihistamine medications were associated, respectively, with a 2.4- and 3.4-fold, increased risk for road crashes.

The studies reviewed in this section, even if varying in the prevalence of OSAS among drivers (possibly explained by different diagnostic or questionnaire methods or confounded or masked by short sleep duration/sleep deprivation) reveal an elevated risk of road crashes of apneic patients. Sleepiness at the wheel is obviously a key symptom worthy of investigation in conjunction with the presence and severity of OSAS (AHI ≥30 or in some studies AHI ≥10 or 15). Nonetheless, the overall importance of the confounding variables of short sleep duration/sleep deprivation and medications, especially as it relates to the driving risk of commercial drivers and for whom the meta-analysis of Ellen et al. (2006) was less convincing, requires further investigation. Evident from the review of the relevant published literature is the fact that many studies addressing the relationship between OSAS and other sleep disorders are too narrowly focused thereby limiting their usefulness. They fail to simultaneously assess and evaluate other important variables, such as other existing medical conditions, medication use, demographic factors, and the relative role each may play in causing excess fatigue and increased driving crash risk. We recommend this deficiency be remedied in the future through multidisciplinary investigations that comprehensively explore the relative significance of the many potential co-existing variables on driving risk.

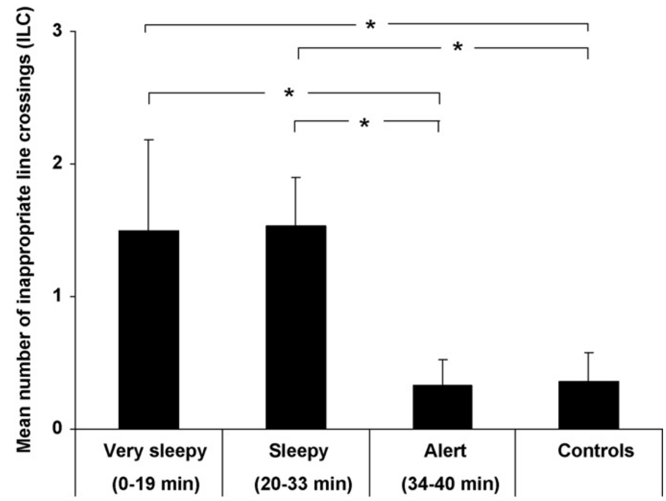

Fig. 2. Number (mean ± SE) of inappropriate line crossings (ILC) during real driving in three – very sleepy, sleepy, and alert - sleep latency (SL) groups – and in healthy controls as determined by the Maintenance of Wakefulness Test (MWT) (Philip et al., 2008). The range in the SL of the studied drivers derived by the MWT is shown in parentheses below each respective SL group (the greater the SL, the lesser the sleepiness). *$p < 0.05$ indicates statistical significance between groups.

2.2.2.1. Evaluation of the driving risk of OSAS patients. A variety of strategies have been proposed to evaluate the risk of individuals for drowsy-driving incidents. Lloberes et al. (2000) and Masa et al. (2000) relied on a clinical interview method to assess perceived excessive sleepiness, sleep-disordered breathing, and risk for nodding-off crashes. However, because this strategy relies entirely on one's ability to self-recognize excessive sleepiness plus truthfulness of response, it is unlikely to be consistently reliable, especially when the prime motivation is to maintain one's driving license for employment and independence.

Two objective clinical measures, the MSLT and Maintenance of Wakefulness Test (MWT), are sensitive predictors of daytime sleepiness and driving performance. The MSLT correlates well with self-assessed sleepiness by the ESS, and it shows good dose-response with sleep duration (Punjabi et al., 2003). The limited number of studies thus far conducted show a strong relationship between the MSLT and driving performance. Banks et al. (2005) compared the MWT with driving simulator performance of healthy, sleep-deprived volunteers, showing for the first time evidence of the predictive value of the MWT. Additional studies (Sagaspe et al., 2007; Philip et al., 2008), done in both simulated and real driving environments, have also found that MWT scores are significantly associated with impaired driving, e.g., inappropriate lane-crossings, as depicted in Fig. 2 (Philip et al., 2008). The MWT seems to be a reasonable approach when paired with questionnaires on sleepiness at the wheel to assess the driving risk of apneic patients, but more extensive data are needed to better evaluate its predictive value on driving accident risk for OSAS as well as other sleep-disordered patients. As pointed out by Pack et al. (2006), addressing the impairment of commercial drivers requires assessment of both the problems of insufficient sleep/sleep deprivation and OSAS, the former being more common. The issue of whether OSAS is best assessed by subjective or objective methods remains an open question. However, the availability of an easy-to-administer objective, cost-effective diagnostic test for OSAS would certainly be of diagnostic value and, in addition, help resolve medico-legal issues.

2.2.2.2. Impact of medical treatment for OSAS on driving risk. Since OSAS is known to be an important risk factor for drowsy-driving incidents, a key challenge is how to cost-effectively mitigate it. Haraldsson et al. (1991) studied 15 OSAS male drivers who suffered from sleep spells while driving and 10 matched controls without such spells in an advanced driving simulator. The clinical evaluation was conducted by a questionnaire scoring symptoms of snoring, sleep disturbances, and diurnal sleepiness before and after uvulopalatopharyngoplasty (UPPP) surgery to relieve OSAS-related disturbed sleep. Brake reaction time, lateral position deviation, and driving-off-road events were measured during a 90 min simulated rural drive under twilight conditions. Before UPPP, the patient group showed impaired performance compared to controls, but afterwards reaction time performance improved, with 12 of the 15 OSAS patients showing a marked decrease in sleepiness while driving. For the clinically successful cases, the number of off-road episodes decreased substantially.

In another study by Haraldsson et al. (1995a), the long-term effects of UPPP on driving performance of 13 middle-aged (median 52 years) male patients and five matched controls were tested before and three to four years after surgical intervention. On both occasions, the participants were subjected to an identical low-arousal 90 min test in an advanced driving simulator and daytime polysomnography. They were also asked to self-assess their driving skills and vigilance using a visual analogue scale (VAS). All but one individual reported being a more vigilant and safer driver following surgery. Objective tests showed the initial improvement in brake reaction time, lateral position deviation, and number of off-road incidents was sustained for the three to four-year span following UPPP surgery, but not always in accordance with improvement in the AHI.

To confirm these experimental results, Haraldsson et al. (1995b) compared the driving accident rate of apneic patients who showed symptoms of heavy snoring, sleep disturbances, and daytime sleepiness over a five-year period before and after UPPP. Data were collected by questionnaire from 46 patients who had undergone surgical intervention and 142 non-apneic matched controls. Following surgery, self-reported sleepiness while driving decreased in 87% of the OSAS patients ($p < 0.001$), and traffic crashes (corrected for mileage driven) declined nearly four-fold compared to controls ($p < 0.001$). Further, the relative rate of patient involvement in any single-car crash fell by 77% ($p < 0.05$), and the relative rate of single-car accidents declined by 83% ($p < 0.001$).

Today, continuous positive airways pressure (CPAP) treatment has supplanted UPPP as the primary therapy of OSAS, and several studies have investigated its impact on drowsy-driving incidents. Krieger et al. (1997) studied 547 patients who made up a larger clinical case series of 893 OSAS patients undergoing CPAP treatment and who completed a one-year follow-up assessment. Baseline information was collected by a self-report questionnaire on driving crashes or near misses due to sleepiness in the 12 months before and 12 months after commencement of CPAP therapy. The number of persons who had experienced drowsy-driving crashes was almost halved following treatment, from 60 to 36 ($p < 0.01$), and the number of patients who had near-miss crashes decreased nearly five-fold, from 151 to 32 ($p < 0.01$). The average number of crashes/patient also declined, from 1.6 ± 1.3 to 1.1 ± 0.3 ($p < 0.01$), as it did for near-miss incidents, from 4.5 ± 6.5 to 1.8 ± 1.4 ($p < 0.01$). The cost was quantified in terms of the number of days of hospitalization as a consequence of the driving crashes; the before-to-after CPAP treatment effect amounted to a more than 10-fold reduction in hospital days, from 885 to 84. George (2001) also assessed the effect of CPAP therapy on road crashes, based on municipal motor vehicle accident records, among 210 professional and non-professional drivers suffering from OSAS and an equal number of control drivers. CPAP therapy was associated with an OSAS crash rate on par with normal drivers, whereas the crash rate for a subgroup of 27 drivers who were untreated for OSAS remained high and unchanged.

Although CPAP is the current treatment of choice for OSAS, it is cumbersome and noisy, giving rise to the risk of poor compliance. Over the past few decades, there has been mounting interest in oral appliances (OApps) to manage snoring and OSAS (Ng et al., 2005; Hoffstein, 2007; Hoekema et al., 2008; Ghazal et al., 2009). OApps exert their therapeutic effect by advancing the mandible and preventing the tongue from obstructing airflow, thereby preserving airway patency during recumbent sleep. Various OApps are currently available, and most seem to be an attractive alternative to CPAP in that they are simple, unobtrusive, quiet, non-power-source-dependent, and economical. Randomized controlled trials confirm OApps therapy is effective for as many as 50% of all OSAS patients, being especially beneficial in mild and moderate cases by reducing snoring and the AHI, as determined by polysomnography, and daytime sleepiness, as self-assessed using the ESS (Chan et al., 2007; Hoffstein, 2007).

We were able to find only a single investigation in the published literature pertaining to the impact of OApps on driving performance (Hoekema et al., 2007). In this study, OSAS patients ($n = 20$) and controls ($n = 16$) were evaluated by a 25 min simulated driving test. After randomization, two groups of 10 patients commenced either OApps or CPAP therapy. Following two to three months of the respective treatments, the test was repeated. At baseline, the total number of attention lapses during driving was significantly higher in the OSAS than control group, as expected. OApps and CPAP were equivalent in significantly reducing the total number of attention lapses by OSAS drivers and improving their performance on simulated driving. However, a more comprehensive assessment of the benefit of OApps on simulated and, more appropriately, actual driving performance and traffic incidents is required to properly evaluate their potential role in mitigating the known drowsy-driving risk posed by OSAS.

Overall, the results of the reviewed studies reveal that UPPP, CPAP, and OApps are effective interventions for most persons at risk for drowsy-driving incidents due to OSAS. Nonetheless, although CPAP, in particular, can reduce sleepiness in many OSAS patients, it is not completely effective in all, since some continue to experience excessive daytime sleepiness and fatigue. For these individuals, the relatively new wake-promoting medications of modafinil and armodafinil (R-enantiomer of racemic modafinil) show promise as an add-on treatment. Black and Hirshkowitz (2005) applied the MWT, ESS, Clinical Global Impression of Change (CGIC), and Functional Outcomes of Sleep Questionnaire measures to assess the effectiveness of modafinil for such cases. Compared to placebo, modafinil in a daily dose of 200 or 400 mg significantly improved mean sleep latency on the MWT, sleepiness on the ESS, and overall clinical condition on the CGIC. On an individual basis, modafinil was effective in improving wakefulness in ~60% of the CPAP-treated patients with residual excessive sleepiness. Comparable results were also found with armodafinil in patients poorly responsive CPAP. Hirshkowitz et al. (2007) found a 150 mg daily dose of armodafinil improved daytime wakefulness and cognition and reduced fatigue. Finally, Roth et al. (2006), involving a larger sample of 395 poorly responsive CPAP patients, found the mean change from the baseline MWT sleep latency across the morning and afternoon was significantly greater with armodafinil than placebo. After 12 weeks of treatment, self-rated sleepiness and fatigue (ESS and Brief Fatigue Inventory) were significantly improved by armodafinil versus placebo. In addition, a statistically significant greater proportion of patients evidenced at least minimal improvement with armodafinil versus placebo on the CGIC measure (72% versus 37%).

The results of these illustrative medication studies on OSAS patients with residual excessive sleepiness despite treatment with CPAP indicate modafinil and armodafinil are useful adjunct therapies. Future studies are encouraged to assess the usefulness of these and other wakefulness-promoting medications as a means of reducing the risk for drowsy-driving crashes of OSAS as well as narcoleptic and other hypersomnic patients.

2.2.2.3. Economic impact of motor vehicle crash reduction of OSAS drivers. Surgical (UPPP) and non-surgical (CPAP, OApps, and medication) interventions have been found to successfully lessen the risk for drowsy-driving incidents due to OSAS. However, a key question is whether public health and clinical programs aimed at reducing sleepy driver incidents yield significant economic impact. Sassani et al. (2004) explored a cost-benefit analysis of CPAP treatment. The authors searched the MEDLINE-PubMed database (1980–2003) to perform a meta-analysis of studies that investigated the relationship between driving crashes and OSAS. Estimates of OSAS-related crashes, costs, fatalities, and their reduction by CPAP treatment, were derived using data from the National Safety Council, and estimation of the annual cost of treating OSAS with CPAP was based on medical reimbursement payments. For the year 2000, alone, more than 800,000 American OSAS drivers were involved in motor vehicle crashes, representing an estimated expenditure of US$15.9 billion and 1400 deaths. The annual expense of treating all the American OSAS drivers with CPAP was an estimated US$3.18 billion. Thus, the authors suggested that CPAP treatment potentially represented a cost-reduction of US$11.1 billion and, in addition, an estimated reduction of 980 deaths yearly. This initial exploratory study suggests CPAP treatment is a cost-effective means of reducing the risk for OSAS-associated drowsy-driver crashes and deaths; however, additional more in-depth studies are required to verify these findings (Sassani et al., 2004) and to explore the cost-benefit of other interventions, including OApps.

2.3. Narcolepsy and hypersomnia

Narcolepsy is a disabling neurologic condition affecting ~1 in 2000 individuals (Mignot, 2004). It is characterized by excessive, oftentimes extreme, daytime sleepiness, cataplexy (attacks involving loss of muscle tone and weakness), and frequent transitions during the daytime between wakefulness and rapid-eye-movement (REM) sleep. The prevalence of narcolepsy combined with cataplexy is estimated to be between 25 and 50/100,000 (Longstreth et al., 2007).

Aldrich (1989) reviewed the sleep-related driving accidents of 424 patients diagnosed with OSAS, narcolepsy, and other disorders of excessive sleepiness as well as a control group composed of 70 persons having sleep disorders without excessive daytime sleepiness. The proportion of persons who experienced sleep-related driving incidents was 1.5–4 times higher in the hypersomnolent patient groups than controls. Although the proportion of patients with sleep-related incidents was highest in narcoleptics, OSAS patients were involved in more sleep-related crashes because of their greater number. Overall, the OSAS and narcoleptic patients accounted for 71% of all the sleep-related driving crashes. Moreover, the proportion of severe OSAS patients who had experienced sleep-related incidents was almost twice that of mild or moderate OSAS ones.

George and Boudreau (1996) compared the performance on the divided-attention driving test by apneics ($n = 21$), narcoleptics ($n = 16$), and sex-matched controls ($n = 21$). Narcoleptic patients were younger and sleepier than the OSAS patients. The average number of tracking errors was much greater, ~3-fold more, in patients than controls (228 ± 145 cm for OSAS versus 196 ± 146 for narcolepsy versus 71 ± 31 for controls; $p < 0.001$). Other studies confirm the significant decrement in the mean level plus substantial inconsistency of cognitive performance of narcoleptics in simulated driving assessment studies (Bartels and Kusakcioglu, 1965; Findley et al., 1995, 1999; León-Muñoz et al., 2000; Kotterba et al., 2004). Nonetheless, there are too few sufficiently large studies, especially prospective population-based ones, to determine with confidence the actual magnitude of risk posed by narcolepsy for nodding-off driving incidents.

2.4. Periodic limb movement disorders of sleep (PLMD) and restless legs syndrome (RLS)

PLMD and RLS are relatively common sleep pathologies, especially in middle-aged and elderly persons (Ulfberg et al., 2001a; Ohayon and Roth, 2002; Portaluppi et al., 2009). Epidemiology studies have found the prevalence of RLS in these age groups to vary between 9 and 20% and the prevalence of PLMD to vary between 4% and 11% (Hornyak and Trenkwalder, 2004). Using a cross-sectional telephone survey conducted in United Kingdom, Spain, Portugal, Italy, and Germany, Ohayon and Roth (2002) found the prevalence of RLS to be 5.5% in the general population, although it was somewhat higher in older persons (>65 years of age) based on the minimal criteria of the International Classification of Sleep Disorders. In Sweden, Ulfberg et al. (2001a) reported the prevalence of RLS to be 5.8% in men, and Ulfberg et al. (2001b) and Wesstrom et al. (2008) reported it to be higher, 11.4–15.7%, in working-aged, especially menopausal, women based on the response of the general population to a distributed questionnaire. In the general population, the prevalence of PLMD is somewhat lower than RLS. Ohayon and Roth (2002) found its prevalence to be 3.9%, but it was somewhat higher in the middle-aged and elderly and in women.

Even though these prevalent sleep disorders can give rise to severe daytime fatigue and somnolence, they have yet to be properly evaluated for the risk each posses for driving crashes. Out of 26 subjects suffering from either PLMD or RLS, Aldrich (1989) reported four subjects who had been involved in traffic crashes. However, it is impossible to conclude from this quite small sample-sized study the actual risk attributed to each of these sleep disorders. Thus, we urge further research be directed to assessing the role of PLMD and RLS in drowsy-driving incidents.

Table 1
Chronic medical conditions that can potentially compromise sleep and/or elevate daytime feelings of fatigue*.

Alcoholism	Hepatic disease
Allergic and non-allergic rhinitis	Huntington's disease
Anemia	Hyperthyroidism
Anorexia	Hypothyroidism
Anxiety syndrome	Illicit drug abuse
Asthma/nocturnal asthma	*Insomnia*
Ataxia	Manic disorder
Bipolar disorder	Metabolic syndrome/obesity
Bulimia nervosa	Migraine
Cancer	Multiple sclerosis
Cerebrovascular disease	*Narcolepsy*
Chronic fatigue syndrome	Nocturia
Chronic pain syndromes	*Obstructive sleep apnea syndrome*
Clinical depression/major depressive disorder	Osteoarthritis
COPD (Bronchitis and Emphysema)	Parkinson's disease
Coronary heart disease	Peptic ulcer disease
Dementia	*Periodic limb movement disorder*
Diabetes	Renal failure
Dyskinesia	Respiratory failure
Dystonia	*Restless legs syndrome*
Epilepsy	Rheumatoid arthritis
Gastroesophageal reflux disorder	Schizophrenia
Head trauma	Spastic torticollis
Heart failure	

* Italics denote clinical sleep disorders

3. Chronic medical conditions and daytime fatigue

3.1. Non-primary sleep disorders

Many medical conditions not classified as sleep disorders may, nonetheless, be a significant source of excessive daytime fatigue, compromised cognitive functioning, and drowsy driving. Table 1 lists some of these. The list, although appearing extensive, is intended to be illustrative rather than exhaustive, since nearly all acute and chronic medical conditions have the potential, directly or indirectly, to affect one's quality/quantity of nighttime sleep, daytime alertness, and/or energy level.

The exact genesis of the elevated level of daytime fatigue from the different medical conditions is diverse and often unknown. It may be the direct consequence of the psychosocial impact of the altered health status, i.e., psychological stress emanating from loss of self-esteem and independence and/or the constant and severe frustration and hopelessness of no future improvement (e.g., severe rheumatoid arthritis/osteoarthritis, multiple sclerosis, depression), disruptive and energy-draining effect of the pathophysiology of the disease state (e.g., anemia, cancer, chronic pain, metabolic dysfunction), nocturnal timing or worsening of symptoms that disrupt nighttime sleep (e.g., asthma, gout, peptic ulcer, acid reflux disorder, urticaria), and/or adverse effects of medications (Zwarts et al., 2008). The literature is convincing that numerous medical conditions are linked with elevated daytime fatigue. However, a variety of issues cloud the exact interpretation of the nature and severity of the generated fatigue as well as its pertinence to the risk for driving crashes. Moreover, a review of the multitude of studies addressing the fatigue of chronic medical conditions, other than sleep disorders, brings to light not only the inconsistency and great diversity of the manner in which fatigue is conceptualized, defined, and investigated but also the numerous potential sources of fatigue that are not typically considered in the epidemiology of drowsy-driving incidents.

These issues are clearly exemplified by studies of arthritic diseases. The working definition of fatigue in some studies is the self-perceived level of physical discomfort or pain (e.g., Riemsma et al., 1998). In others, it is the level of emotional (psychosocial) stress, reported by patients as energy draining, worry, hopelessness, and depression (e.g., Mancuso et al., 2006). In still others, the exact definition of fatigue is lacking altogether (e.g., Wolfe et al., 1996; McCarley et al., 2007), with the gathering of patient-defined subjective (VAS) self-assessments of its intensity and specific measures of disease activity, depressive mood, and psychosocial support used to derive dependent or predictive variables (e.g., Huyser et al., 1998; Power et al., 2008; Hewlett et al., 2005; Repping-Wuts et al., 2007, 2008). Moreover, the investigative protocols and methods have varied extensively, i.e., from clinical case series studies involving questionnaires or direct interviews to population-based telephone and other surveys. Complicating matters further is the fact that almost all the investigations have neglected the potential adverse effect of medications and their dose as sources of the assessed elevated fatigue, sleepiness, and drowsy-driving risk. Thus, it is unclear to what extent the reported increased fatigue level represents the multi-dimensional attributes of a given medical condition, undesired effect of medications, or patient response (i.e., frustration, worry, and/or social isolation) to being ill, or all of these variables plus others.

We have chosen to discuss the linkage between health status and complaints of elevated fatigue level by highlighting the extremely prevalent chronic medical conditions of allergic and non-allergic rhinitis, bronchial asthma, chronic obstructive pulmonary disease, and rheumatoid arthritis/osteoarthritis, and, in addition, chronic fatigue syndrome (CFS). Even though CFS is much less prevalent than the other conditions, it is relevant because of its persisting excessive daytime fatigue. With perhaps the exception of CFS, these selected medical conditions are neither categorized as sleep disorders nor appropriately appreciated by the clinical community as significant causes of compromised sleep and sources of excessive daytime fatigue, somnolence, and drowsy driving. We emphasize that four of the five considered medical conditions are extremely prevalent in the driving population, exhibit a nocturnal timing in the manifestation or peak intensity of symptoms, and give rise to elevated daytime fatigue, sleepiness, and compromised cognitive performance.

3.2. Allergic (AR) and non-allergic rhinitis (NAR)

AR, a very common medical condition affecting >50 million Americans, is triggered by specific environmental allergens that activate the immune system causing inflammation and copious secretion of mucus by glands of the upper airways. NAR is also an inflammatory condition of the upper respiratory track, but not necessarily triggered by specific antigens, that primarily affects adults. The main symptoms of both AR and NAR are nasal swelling, congestion, and drainage, with other possible ones being itching of the eyes, ears, mouth, and throat. The symptoms of AR are typically restricted to specific seasons of the year, while those of NAR tend to persist throughout the year.

The severity of the nasal congestion of both AR and NAR exhibits rather profound 24 h variation. Typically, it is most intense during the overnight period of sleep (Smolensky et al., 1995, 2007). Clinical and population-based investigations (Juniper and Guyatt, 1991; Young et al., 1997b; Craig et al., 1998; Staevska et al., 2004; Léger et al., 2006b; Udaka et al., 2007) show it can dramatically disturb nighttime sleep and even manifest as OSAS, resulting in excessive daytime sleepiness, fatigue, and cognitive impairment. Indeed, nasal obstruction is an independent risk factor for OSAS, even in the non-obese (Staevska et al., 2004). In a large population-based American epidemiology study ($n > 4900$), Young et al. (1997a) found, in comparison to controls, that AR sufferers who consistently or often experienced nighttime symptoms of nasal congestion (≥5 nights/month) were significantly more likely to experience habitual snoring (≥3 nights/week), chronic excessive daytime sleepiness, or chronic non-restorative sleep. Furthermore, those reporting nasal congestion were almost two-fold more likely to experience moderate to severe sleep-disordered breathing than those not reporting it. Another large population-based Japanese epidemiology study (Udaka et al., 2007) of AR ($n > 4800$) found the odds ratio to be 5.22 for habitual apnea and 2.17 for daytime sleepiness (ESS) in those who did versus did not experience chronic nasal obstruction. In spite of these findings, the impact of the elevated fatigue and compromised cognitive status of AR and NAR on driving ability and risk for drowsy-driving crashes remains to be assessed.

Antihistamine, anti-inflammatory, and decongestant medications are typically used to manage the symptoms and underlying pathophysiology of AR and NAR. Antihistamine medications, especially the first generation formulations, are known to impair cognitive performance and vigilance and even be sleep-promoting. While past studies have primarily focused on the potential cognitively impairing effects of the older generation sedating and new-generation non-sedating antihistamine medications upon simulated (e.g., Gengo et al., 1990; Potter et al., 2003) or actual highway driving (e.g., Ramaekers et al., 1992; O'Hanlon and Ramaekers, 1995; Theunissen et al., 2004; Verster and Volkerts, 2004), we were unable to locate any studies in the published literature pertaining to the impact of AR and NAR, themselves, on driving crash risk. Such studies are long overdue, given their high prevalence in the driving population.

3.3. Asthma

Asthma affects ∼16 million American adults and is characterized by chronic inflammation, smooth muscle spasm, and copious mucous secretion by the glands of the small airways of the lung. The narrowed and mucus-obstructed airways elevate resistance to airflow, making breathing labored, and give rise to the characteristic symptoms of chest tightness, shortness of breath, and cough/wheezing. Asthma is typically triggered by environmental or food antigens, certain medications, or exercise, although the exact triggers may be unknown. The occurrence and severity of asthma symptoms and attacks exhibit profound 24 h patterning (Smolensky et al., 1986, 2007). Asthma is primarily a nighttime medical problem. In most asthmatics, the risk of an attack is several-hundred-fold greater around 4–5 a.m. than around 1–2 p.m. (Dethlefsen and Repges, 1985), and epidemiology studies indicate that ∼75% of asthmatics are likely to experience dyspnea (difficult/labored breathing) primarily or only during the nighttime, causing disruption of sleep at least once/week (Turner-Warwick, 1988).

The sleep of asthmatic persons may be significantly impaired several nights each week, especially if the condition is severe or under-treated (Turner-Warwick, 1988). Repeated nocturnal awakenings due to breathing distress compromise the quantity and quality of nighttime sleep, resulting in elevated daytime fatigue, tiredness, and compromised mental/cognitive fitness (Turner-Warwick, 1988; Fitzpatrick et al., 1991; Brown et al., 1993; Van Keimpena et al., 1995; Janson et al., 1996). The study by Fitzpatrick et al. (1991) on a small clinical sample of asthmatic adults (median age 43 years) found both poorer subjective and objective sleep quality, the latter manifested as longer sleep latency, reduced stage four (deep) sleep, and more time awake (median difference 51 min, compared to non-asthmatic controls. As a consequence, nocturnal asthmatic subjects have been found to be slow in completing trail-making cognitive tests and to score poorly on paced serial addition tests. A larger study by Janson et al. (1996) of adults participating in the European Community Respiratory Health Survey found that problems in inducing nighttime sleep plus undesired early morning awakenings were nearly twice as great in asthmatics than non-asthmatics, resulting in daytime sleepiness being 50% more common in asthmatics. Hower, as in the case of AR and NAR, the risk for driving accidents due to the elevated daytime tiredness, fatigue, and compromised cognitive status caused by the disruption of sleep by nocturnal asthma has yet to be appropriately assessed, either through driving simulator, naturalistic, or population-based studies.

3.4. Chronic obstructive pulmonary disease (COPD)

COPD – a chronic, progressive and debilitating obstructive pulmonary disease that affects ∼14 million American adults – compromises O_2 and CO_2 exchange between the alveoli and pulmonary blood circulation as a result of irreversible damage to respiratory tissue. COPD manifests as chronic bronchitis, with symptoms of chronic cough, excessive mucus production, and shortness of breath, and emphysema, with shortness of breath as the primary symptom. The most common cause of COPD in ∼95% cases is tobacco smoking. Smoking is quite common in commercial transport drivers (Zuskin et al., 1994), suggesting this primarily male, blue-collar working population may be particularly at risk for COPD.

Numerous studies document COPD is associated with insomnia and altered sleep physiology and quality, i.e., frequent sleep arousals and nocturnal hypoxemia (Douglas, 1998; Fanfulla et al., 2004; Kutty, 2004). Although elevated fatigue level is a typical and prominent symptom of COPD, its exact origin – mental, physical, or otherwise – in individual sufferers, particularly in working-aged persons, is often unknown. Furthermore, even though numerous quality of life studies reveal the broad spectrum of deleterious effects of COPD, the impact of this prevalent lung disease on driving competency and driving crash risk is far from clear.

Theander and Unosson (2004) used the Fatigue Impact Scale to study the perception and impact of excess fatigue on the everyday life of COPD sufferers ($n = 36$) and age- and sex-matched controls ($n = 37$). Some 47% of cases, compared to 13.5% of controls, reported an abnormal fatigue level every day the preceding month. The duration of the self-assessed (subjective) fatigue amounted to >6 h/day in more than half of the COPD sufferers, with complaint of significant effect on cognitive, physical, and psychosocial functioning. Liesker et al. (2004) found that even stable, non-hypoxic COPD participants performed significantly poorer than age- and intelligence-matched controls on several measures of cognitive performance, e.g., trail making B, digital symbol, and addition tests, thereby suggesting at least certain aspects of cognitive functioning in COPD are not always the result of hypoxemia. In a comprehensive assessment of 130 COPD subjects, Kapella et al. (2006) collected information on a range of variables using the Numerical Rating Scale (to gauge the frequency, intensity, and distress of fatigue and dyspnea), Fatigue Assessment Scale, Chronic Respiratory Disease Questionnaire, Profile of Mood States, Pittsburgh Sleep Quality Index, Functional Performance Inventory, and spirometry (to assess respiratory dysfunction). Fatigue was found to be situation-specific, closely correlated with dsypnea, and responsive to rest and sleep. The severity of dyspnea, depression, and reduced sleep quality accounted for 42% of the total variance in subjective fatigue level, while the severity of dyspnea, airflow obstruction, and anxious mood accounted for 36% of the total variance in functional performance.

The literature addressing the effect of COPD and its associated elevated fatigue level on driving incidents is sparse, as we were only able to locate a single, small-sized sample publication. Pretto and McDonald (2008) found the simulated driving performance and neurocognitive functioning of hypoxemic COPD licensed drivers were impaired and unimproved by oxygen supplementation. In spite of the extensive number of studies that document COPD is a major cause of poor nighttime sleep and daytime fatigue and cognitive impairment, almost nothing is known about its impact on drowsy-driving crash risk of non-professional drivers or commercial transport workers, who because of their demographic characteristics are likely to be smokers and suffer from bronchitis and emphysema (see Di Milia et al., 2011).

3.5. Rheumatoid arthritis (RA) and osteoarthritis (OA)

RA is an autoimmune disease affecting ∼1.3 million American adults, manifesting as chronic inflammation and deformity of affected joints. Its major symptoms are localized swelling, pain, and stiffness. RA typically develops between 35 and 50 years of age (although it can be problematic even in adolescents and young adults as juvenile RA) and is 2–3-fold more common in women than men. However, OA is the most common form of arthritis, affecting ∼27 million middle-age and elderly adults in the USA. OA has a different etiopathology than RA. The pain, swelling, and immobility of OA result from breakdown of cartilage within the joints from repeated use and aging. OA can commence as early as 40–50 years of age and progressively worsen thereafter. Both RA and OA may co-exist in the same person. According to Abad et al. (2008), arthritis is the leading cause of chronic illness in the USA with 72% of adults ≥55 years of age diagnosed with its various forms reporting sleep problems. Clinical studies reveal the intensity of RA and OA symptoms exhibits substantial day-night variation; in diurnally active persons RA symptoms are typically most intense early in the morning, while OA symptoms tend to be most intense late in the afternoon and at night (Kowanko et al., 1982; Bellamy et al., 1990, 1991; Hardo et al., 1992). Although the focus of the discussion here is RA and OA, other arthritic conditions of lower prevalence, such as juvenile RA, Sjogren's syndrome, systemic lupus erythematosus, scleroderma, Behcet's disease, seronegative spondyloarthropathies, sarcoidosis, and fibromyalgia, also may compromise nighttime sleep and result in elevated daytime fatigue (Abad et al., 2008).

Wolfe et al. (2006) used the Medical Outcomes Study Sleep Questionnaire plus a VAS sleep disturbance scale to assess and compare the sleep of RA patients ($n = 8676$) and a comparison group ($n = 1364$) unaffected by fibromyalgia or inflammatory conditions. The sleep and VAS disturbance values of the RA cohort exceeded those of the normative (control) population by 25% and 42%, respectively, and this was attributed to the pain, depressive mood, and disease activity of RA. Comparable results were found by Power et al. (2005) from their cross-sectional sampling of 118,336 adults who participated in the 2000/2001 Canadian Community Health Survey. The prevalence of insomnia symptoms and complaint of non-restorative sleep, caused at least to some extent by the pain of RA was, respectively, 24.8% and 11.9%, which was significantly greater than in the non-RA-reference group. These findings are consistent with those of Ohayon (2005) derived from a community-based telephone survey of more than 18,000 Europeans. Chronic painful physical ailments, e.g., of the back and joints, of >6 months duration were significantly associated with difficulty in initiating sleep in 5.1%, maintaining sleep continuity in 7.5%, early morning awakenings in 4.8%, and non-restorative sleep in 4.5%. The sleep disturbances of RA, commonly assessed by subjective questionnaires, have also been confirmed by the objective method of wrist actigraphy (Lavie et al., 1992).

Fatigue is one of the most frequently reported symptoms of RA. However, its conceptualization in terms of origin (disease activity, pain, compromised sleep quality/quantity, etc.) and type (physical, emotional, etc.), when assessed by self-rating VAS and numerical rating scales, are typically undefined. This was especially the case in early studies. Hewlett et al. (2005), Repping-Wuts et al. (2008), and Power et al. (2008) have attempted to remedy this deficiency by determining its exact nature and dimension.

Repping-Wuts et al. (2008) studied 29 RA patients, first having them complete questionnaires on fatigue severity, overall disability, quality of life, sleep disturbance, and disease activity, and then interviewing each to obtain specific verbal descriptions. Fatigue was reported to be a physical experience (i.e., pain, disability, etc.) of variable intensity and duration that influenced everyday tasks, attitudes, and leisure time; further, the sudden onset and exhausting nature of RA-induced fatigue was self-perceived and expressed as frustrating and anger-inducing. Hewlett et al. (2005) interviewed 15 individuals with significant RA-caused fatigue to gather information about its description, cause, and consequence. Two types, 'severe weariness' and 'dramatically overwhelming', of fatigue were expressed. Participants of this study further described their fatigue as having physical, cognitive, and emotional components attributable to the inflammation and difficult movement of their joints and to non-refreshing sleep. The reported effects were far-reaching, negatively affecting physical activities, emotions, relationships, and social and family roles.

Power et al. (2008) explored the dimension and definition of fatigue of 28 men and 18 women (average age 72.3 years) with symptomatic hip or knee OA in a community setting. Participants completed a series of questionnaires, including ones to assess the severity of their OA, depression, and fatigue. Participants communicated their fatigue using the words 'exhaustion', 'being tired', and 'coming up against a brick wall'. Participants reported the fatigue affected their physical functioning, participation in social activities, and ability to do household chores, and it was perceived as being different from sleepiness, with participants distinguishing between its two different, i.e., mental and physical, forms. Factors believed to increase fatigue included OA pain, pain medications, advanced age, certain weather conditions, and poor sleep. Mental health was identified as both affecting and being affected by the fatigue.

There is no doubt that RA and OA can be a significant source of one or more forms of fatigue, which constitutes a meaningful predictor of work dysfunction, health impairment, and depressive mood (Belza, 1995; Wolfe et al., 1996, 2006; Power et al., 2008). Belza (1995) compared the self-reported fatigue of 51 adult RA sufferers with 46 age- and sex-matched healthy controls without RA using a series of questionnaires: the Multi-dimensional Assessment of Fatigue Scale, Sleep Survey, Health Assessment Questionnaire, and Profile of Mood States. Fatigue scores of the RA subjects were significantly greater than controls and were strongly associated with poor sleep, functional disability, pain level, and depressive mood. Wolfe et al. (2006) evaluated the sleep of 8676 RA patients and a comparison group of 1364 control subjects with non-fibromyalgia, non-inflammatory disorders using the Medical Outcomes Study (MOS) sleep questionnaire and a VAS. Sleep disturbance was greater in the patient group, with scale values of the MOS and VAS ratings exceeding population norms by 25% and 42%, respectively; multivariate analyses determined the causes of the disturbed sleep to be disease activity, pain level, and mood state.

The definition of fatigue expressed by RA sufferers differs greatly from that expressed by otherwise healthy persons and sleep-disordered patients, i.e., sleepiness or loss of alertness. It also differs markedly from that used in industrial medicine, as discussed in other articles of these proceedings (e.g., Williamson et al., 2011). Such divergent conceptualizations of fatigue further complicate the evaluation of the relevant literature, especially in regard to the role that excessive fatigue might play in road crash risk across various illnesses and driver groups. Given the high prevalence of RA and OA in the driving population and its link to some form of expressed fatigue, it is disappointing that there has been so little investigation of fatigue-related motor vehicle accidents associated with these medical conditions and their medical treatments. Although some studies have explored the epidemiology of driving crashes in the elderly, generally in those >65 years of age (McGwin et al., 1999, 2000; Hours et al., 2008), they did not assess the role of their chronic medical conditions specifically in terms of excessive fatigue and sleepiness as risk factors. Obviously, appropriate population-based studies are urgently required to assess the potential risk of RA and OA and their prescribed and over-the-counter medications for fatigue-related driving risks.

3.6. *Chronic fatigue syndrome (CFS)*

CFS is a complex medical condition. In addition to the central complaint of severe and persisting fatigue, there are eight additional agreed upon clinical symptoms that typically vary in expression and intensity over time. These include loss of memory/concentration, sore throat, painful and mildly enlarged lymph nodes of the neck/axillae, unexplained muscle pain, pain that moves between joints without swelling or redness, headache, non-refreshing sleep, and extreme exhaustion lasting >24 h following taxing physical or mental exertion. Other symptoms may include psychological ones (e.g., depression, mood swings, irritability, and anxiety), atypical allergic sensitivities, visual disturbances, and gastrointestinal complaints. Generally, the clinical diagnosis of CFS is made when a patient presents with new- or definite-onset persisting fatigue along with four or more of the aforementioned characteristic symptoms and after the exclusion all other potential diagnoses (http://www.cdc.gov/cfs/cfsdefinitionHCP.htm, accessed August 13, 2009). There has been continuing and as yet unresolved medical controversy as to whether CFS is a catch-all label for a variety of ailments of different origin, each having in common severe and persisting fatigue, or if it is a unique disease described by inflammatory, oxidative, and nitrosative stress pathways (Maes, 2009). Independent of one's perspective, CFS is characterized by a chronic disabling and severe fatigue that by definition persists for >6 months (Fukuda et al., 1994). According to Steele et al. (1998), CFS affects ~4.2% of the adult population. In primary-care practice, however, its prevalence has been reported to be greater, 11.3%; although, after more comprehensive diagnostic investigation, it was found to be much lower in prevalence, 2.6%, (Wessely et al., 1997).

It is not yet clear whether sleep disturbances are central to CFS or if both CFS and sleep disorders share a common underlying cause. Several clinical studies have attempted to clarify the relationship between sleep disturbances and CFS, but without definite conclusion. Farmer et al. (1995) reported that 80% of CFS patients have a clinical sleep disorder, but other studies (Krupp et al., 1993; Sharpley et al., 1997) are much more conservative. Thus, as found with insomniacs, the subjective complaints of poor and non-refreshing sleep by CFS patients are not always confirmed by polysomnography (Sharpley et al., 1997). Nonetheless, CFS sufferers, with or without co-existing mood disorders, do experience difficulty initiating and maintaining sleep (Fishler et al., 1997; Morriss et al., 1997). As is the case with all depressive disorders, depressed CFS compared to healthy non-depressed individuals experience poorer sleep efficiency (Morriss et al., 1993; Sharpley et al., 1997) and shorter REM latency (Morehouse et al., 1998), although the latter is not a consistent finding. Other changes in sleep architecture, for example, in alpha EEG patterning, are thought to be present in CFS, although even this is debated (e.g., Dauvilliers and Touchon, 2001; Majer et al., 2007).

A key question is whether sleep disturbances cause CFS or CFS causes sleep disturbances. No definitive conclusions can be drawn at this time. In some cases, sleep disturbances negate the diagnosis of CFS, while in other cases sleep disturbances may exacerbate its fatigue (Morriss et al., 1997). Many CFS sufferers nap or rest during the daytime because of their perceived overwhelming fatigue. This practice aggravates the complaints of nighttime sleep disturbances and results in further daytime fatigue. Thus, a vicious cycle is established that may contribute to the chronic fatigue, particularly as it leads to increasing inactivity. The latter, in turn, can result in neuromuscular deconditioning, which brings into play other mechanisms, sources, and types of fatigue. Given the increasing attention given to CFS, we find it unacceptable that there is an absence of literature pertaining to the risk CFS presents for drowsy-driving incidents.

4. Discussion

The evidence is compelling that severe daytime sleepiness, tiredness, and/or fatigue – whether the result of a primary sleep disorder or an acute or chronic medical condition – can compromise the cognitive performance of commercial and non-commercial drivers and contribute to traffic crashes. However, we have argued in this article, which pertains specifically to certain selected sleep disorders and medical conditions, and also elsewhere (Di Milia et al., 2011) that a major limitation of determining the relative risk for fatigue in traffic crashes is the lack of a mutually agreed upon conceptualization and definition of fatigue across the many different disciplines and investigators involved with its study. It should be readily apparent from the synopsis of the diverse studies presented in this article, as well as other articles of this special issue, that fatigue is defined in quite disparate ways by different investigators and disciplines. In some studies it is represented by self-rated estimates of one's tiredness, sleepiness, or decreased alertness (Randler, 2008; Di Milia and Bohle, 2009). In others it is framed in terms of physical discomfort/pain (Riemsma et al., 1998), hypoxia/dyspnea (Liesker et al., 2004; Kapella et al., 2006), or abnormal MSLT and MWT (Banks et al., 2005; Sagaspe et al., 2007; Philip et al., 2008). Finally, in some studies it is entirely undefined, instead relying on the participants to self-define it and its severity using different and individualized criteria (e.g., Wolfe et al., 1996; McCarley et al., 2007). Thus, it is not surprising that estimates of fatigue-related driving incidents can be inaccurate and vary so widely. Deficiencies and inconsistencies in the definition of fatigue and the methods used in its study make it impossible to gain a thorough understanding of the actual role that it plays in driving and other accidents, and these drawbacks thwart the development and application of effective counter measures to diminish its impact, as discussed by Di Milia et al. (2011).

Fatigue is a complex construct, with often extensive differences in its conceptualization and methods of investigation between the various individual disciplines involved in its study. Our extensive review of the literature indicates much of the research of fatigue and its end-effects has been conducted independently by investigators schooled in single disciplines. Lacking are multidisciplinary studies that are designed and conducted to comprehensively assess the various facets of the genesis and outcomes of fatigue, in particular, on crash risk. In another article of these proceedings, we discuss the great many endogenous (biological) and exogenous (environmental) factors that can potentially modify one's fatigue level (Di Milia et al., 2011). We believe wider acceptance of the fact there are many diverse sources and forms of fatigue as well as many endogenous and exogenous factors that influence its effects and intensity will serve to better inform the comprehensive conceptualization of fatigue and design of future multidisciplinary investigations.

What seems to be clear is that insomnia and severe sleep disorders, as exemplified by OSAS, significantly increase daytime fatigue, sleepiness, and risk of drowsy-driving crashes. Indeed, fatigue levels are elevated in cases of severe OSAS, especially in the presence of inadequate sleep/sleep deprivation. Fortunately, OSAS and certain other sleep disorders are responsive to treatment. UPPP and CPAP have been shown to significantly improve the quality of nighttime sleep and daytime vigilance, and most importantly they appear to help mitigate the risk for drowsy-driving crashes in most, although not all, OSAS patients. Indeed, Sassani et al. (2004) suggest CPAP is a cost-effective clinical counter measure for OSAS, capable of reducing the risk and financial cost of drowsy-driving crashes as well as loss of lives. New-generation medications that promote wakefulness, such as modafinil (Black and Hirshkowitz, 2005) and armodafinil (Hirshkowitz et al., 2007), offer hope to drivers who complain of daytime sleepiness, tiredness, and fatigue because they do not derive sufficient benefit from CPAP or UPPP. However, these medications have only recently become available and require more extensive assessment of their utility through well-designed and appropriate sized studies. Other sleep disorders, such as narcolepsy, PLMD, and RLS, also seem to constitute elevated risks for road crashes; yet, these have been the subject of far less study than OSAS and require further detailed evaluation.

Many prevalent medical conditions, such as the ones listed in Table 1, and medications can cause or contribute to elevated or excessive daytime fatigue and drowsy driving. We presented the examples of allergic rhinitis, nocturnal asthma, rheumatoid arthritis/osteoarthritis, chronic obstructive pulmonary disease (emphysema and bronchitis), and chronic fatigue syndrome, which in the aggregate impact a very large proportion of drivers. These diseases are differentially distributed by sex, age, and for some by economic status. Asthma is more likely to affect young drivers, generally those under 25–30 years old, while RA, OA, COPD, and CFS tend to affect middle-aged and older drivers, generally over 40 years of age. More women than men are affected by RA, while more men than women are affected by COPD. Moreover, today COPD is more likely to be found in blue-collar and lower social economic status (SES) workers, which includes professional/commercial drivers. The contribution of excessive fatigue by these and other widespread medical conditions to drowsy-driving traffic incidents seems to be largely unappreciated and not yet adequately addressed.

It is astonishing that only a relatively small number of case-control, population-based, epidemiology studies have focused on the potential involvement of medical conditions and/or prescription and over-the-counter (nonprescription) medications in road crashes. All previous investigations have entailed cohorts of surviving at-fault drivers ≥65 years of age, an age group that tends be over-represented in traffic crashes. The findings reveal an increased odds ratio for those with existing heart disease, hypertension, previous stroke, or arthritis in women (McGwin et al., 2000; Hours et al., 2008), but not diabetes (McGwin et al., 1999). The study by McGwin et al. (2000) also explored the association between medications and automobile crashes, showing a statistically significant elevated odds ratio for drivers using non-steroidal anti-inflammatory, anticoagulant, and angiotensin converting enzyme inhibitor antihypertensive medications. However, a reduced odds ratio was found for those treated with vasodilator and calcium channel blocker antihypertensive medications.

Unfortunately, the findings of these types of studies raise more questions than they answer. A major deficiency is they focus entirely on the survivors of at-fault driving crashes; the findings might be different if studies were prospective and longitudinal in design so that health status and other variables, representative of both survivors and non-survivors of transportation incidents, were assessable. Further, it is unclear whether the use of a specific medication by an at-fault driver constitutes a surrogate variable for a particular medical condition and/or its severity, or whether it constitutes an independent risk factor, itself. Indeed, neither McGwin et al. (2000) nor any other investigators (e.g., Hours et al., 2008) addressed the potential confounding and interactive influences of medical condition, medications (including dose), and the classic demographic variables of age, sex, race/ethnicity, social economic status (e.g., education and income), and partner/marital status, simultaneously (see Di Milia et al., 2011). Moreover, in relation to the theme of this and other articles of these proceedings, the types of epidemiologic studies thus far conducted have yet to specifically assess the role played by the fatigue induced by medical conditions and their treatments on road incidents. Thus, we endorse the conduct of prospective, longitudinal, population-based, multidisciplinary investigations in the future to examine groups of at-fault drivers who did as well as did not survive their crashes to comprehensively explore the role of driver fatigue and related variables.

A major current challenge is how to easily and reliably identify in a cost-effective manner those at risk for drowsy-driving road crashes. Self-assessment scales are not always useful and applicable to everyone. They tend to be less reliable and accurate when applied to men than women, either because men are unable to recognize fatigue as well as women and/or because men are less willing to admit to it (Fjell et al., 2008). Therefore, the supposition of Lloberes et al. (2000) and Masa et al. (2000) that a clinical interview can adequately assess excessive sleepiness to predict sleep-disordered breathing and identify driving risk is suspect, especially when one's prime motivation is to maintain driving status. Two objective measures, the MSLT and MWT, show great promise in predicting fatigue, daytime sleepiness, and drowsy driving. The MSLT correlates well with self-assessed ESS (Johns, 1991) and demonstrates good dose-response with sleep duration (Punjabi et al., 2003), and a limited number of studies evidences a good relationship between the MWT and simulated driving performance (Banks et al., 2005; Sagaspe et al., 2007; Philip et al., 2008). However, these objective tests are not readily available and are costly and time-consuming to administer. Moreover, threshold levels of fatigue assessed by the MSLT, MWT, or other measures in terms of crash risk have yet to be explored. In fact, still to be determined is whether it is possible to derive population norms for such measures to use in the identification of at risk drivers while taking into account individual differences in tolerance and coping skills against fatigue.

In conclusion, in this article we examined several common sleep disorders plus a group of medical conditions known to be highly prevalent in the driving population and which can give rise to atypical levels of daytime tiredness and fatigue. Although sleep disorders and certain classes of medications are increasingly being recognized as risk factors for driving incidents, other medical conditions and their therapies are largely unappreciated as important potential risk factors. While much progress has been made in understanding the link between sleep disorders and driving accident risk, several areas require immediate attention.

- At the diagnostic level, there is as yet no simple reliable and objective measure or tool (e.g., equivalent to breathalyzer for alcohol testing) to quantify *a priori* or *in-situ* the risk for drowsy-driving incidents. A low-cost, simplified "somnotest" is needed to quantify the driver's 'state' in relation to yet to be determined risk thresholds. However, as of now only driving simulators, electroencephalography (EEG), and PERCLOS are used to estimate likely performance, and each has its limitations (see Balkin et al., 2011). Some tests like the MWT and MSLT have been well studied in specific sleep disorders, such as in OSAS, but less so in others. However, they require special equipment and are expensive to administer.
- Primary-care physicians need to play a greater role in mitigating the risk for drowsy-driving incidents. However, the current curriculum of most medical schools devotes too little time to sleep medicine. Thus, primary-care doctors often fail to recognize the signs and symptoms of patients presenting with acute and chronic sleep disorders or other medical conditions linked with excessive fatigue, impaired driving performance, and road crash risk (Papp et al., 2002; Gelir et al., 2004; Vigg et al., 2005; Bandla et al., 2007). We advocate greater education and training in sleep medicine of doctors, ancillary clinical personnel, and other healthcare professionals, including dentists (Barsh, 1996; Jauhar et al., 2008), to improve detection and prevention strategies. Moreover, we recommend more in-depth training of accident investigators, including municipal personnel, to better recognize and catalogue fatigue-related incidents to improve the quality of local and national databases as well as to better assess outcomes of interventions.
- There is limited information on the association between traffic crashes and some sleep disorders – narcolepsy, PLMD, RLS, insomnia – and a variety of common medical ailments; thus, future prospective population and laboratory investigations are recommended to define the extent of the problem each causes and the cost-effectiveness of clinical and other preventive interventions.
- Medical interventions for OSAS – surgery, CPAP, OApps, and medications – constitute important preventive strategies in mitigating transportation incidents, but there are still too little data, especially in the case of OApps and awake-promoting medications, regarding their capability to reduce drowsy driving events.
- Studying the impact of extensive driving in treated and non-treated sleepy patients is of critical importance to public health, because of the high prevalence of nocturnal breathing disorders and short sleep duration/sleep deprivation found among professional drivers, in particular. Many of the OSAS studies have focused only on OSAS severity and driving risk without assessment of the sleep duration and deprivation of drivers. Future studies must assess as a minimum both of these important variables, since too short a sleep duration may be more critical to risk than the presence and severity of OSAS (Pack et al., 2006).
- Additional studies are needed to better define the phenotype of sleepy patients involved in traffic accidents. If only one of thirty OSAS drivers is the victim of a falling-asleep-related incident, it is urgent to track them and to develop special evaluations plus driving prescriptions, e.g., 'no nocturnal driving', as a means of prevention.
- Finally, we urge greater collaboration among researchers and disciplines to employ a shared conceptualization and definition of fatigue, followed by well-designed and conducted prospective multidisciplinary investigations to enhance their value and utility.

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