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Drugs, Driving and Traffic Safety

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Dedication

To our friends and families

Credits and acknowledgements

Many individuals played instrumental roles in the development and completion of this new volume entitled *Drugs, Driving and Traffic Safety.* This book gives a comprehensive overview of the effects of common diseases and their treatments on driving ability. An enterprise of this sort is challenging, and the editors received a lot of help from several people.

We were fortunate to experience professional and enthusiastic support from Ms Beatrice Menz and Kerstin Tuechert, editors at Birkhauser Verlag. Their commitment to excellence was a strong guiding force throughout the development of this volume. We also want to thank all authors for spending their precious time on contributing a chapter.

Finally, we express our gratitude to our friends and families for their patience and support.

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Preface

The volume *Drugs, Driving & Traffic Safety* covers the impact of various diseases and their treatment on driving ability. Traffic safety is an issue that is becoming increasingly relevant. In 2004, the World Health Organization dedicated the World Health Day to road safety to draw attention to the yearly increasing number of traffic deaths. In addition to alcohol and drugs, various medicinal drugs may affect driving performance negatively. Especially psychoactive drugs, i.e. drugs that exert their activity in the central nervous system, and drugs that affect motor function are of concern. The vast majority of those who use psychoactive medication are ambulant outpatients. This suggests that they also participate in traffic. Throughout *Drugs, Driving & Traffic Safety* you will find evidence that the incidence of medicinal drugs among drivers is estimated between 5 and 35%.

The chapters of *Drugs, Driving & Traffic Safety* have been written by experts in the field who have performed primary research in the areas they cover. The book starts with two introductory chapters that cover driver health and world trends in alcohol and drug impaired driving. Thereafter, nine chapters describe the various ways of examining driving ability. These methodological chapters discuss how experimental evidence can be obtained from laboratory tests, driving simulators and actual driving in normal traffic. Other chapters introduce epidemiological methods to study the effects of drugs on driving safety and traffic accident risk. Finally, blood drug determination after roadside surveying is discussed. The next 13 chapters discuss the most common diseases and their treatments on driving performance and traffic accident risk. Anxiolytics, hypnotics, antidepressants and antihistamines are commonly prescribed psychoactive medication. These chapters will show that not all psychoactive medication is safe if one plans to drive a car. The appendix section of *Drugs, Driving & Traffic Safety* gives an overview of all psychoactive drugs that have been investigated on possible effects on driving and their corresponding classification by the International Council on Alcohol, Drugs and Traffic Safety (ICADTS). A second appendix gives an overview of ICADTS guidelines on experimental studies undertaken to determine a medicinal drug's effect on driving or skills related to driving. The final six chapters of this volume cover the effects of alcohol and illicit drugs on driving ability. Alcohol is still the most common drug observed in impaired drivers. However, other drugs such as cannabis and ecstasy are also determined frequently in blood samples of impaired drivers.

The volume *Drugs, Driving & Traffic Safety* will be an important reference book for traffic safety researchers, and psychiatrists, physicians, general practitioners and pharmacists who have to prescribe or dispense psychoactive medication to patients who want to drive a car. Although not all medical conditions, treatments and illicit

drugs are covered by *Drugs, Driving & Traffic Safety*, the volume is a useful overview of the current state of knowledge on drugs and driving. It is our hope that we have succeeded in producing a useful book. As usual, we welcome communications from our readers concerning our volume.

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Driver health and traffic safety: an overview

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Abstract

Road safety has emerged as a major public health and preventative medicine challenge of the twenty-first century. As rapid demographic changes in health demographics and road utilization progress around the world, it has become clear that a significant number of deaths and injuries occur due to impairments in driver health and wellbeing rather than by purely "accidental" means. While legislative focus on speeding, seat-belt non-use and drunk driving have proven effective in many parts of the developed world, focus is now turning to fatigue and sleep loss, inattention/distraction, risk-taking behaviours and other sources of impairments with a primarily medical basis. Cybernetic traffic safety models consider driving in the context of complex and often stochastic states and many chronic or acute medical conditions, particularly those affecting cognitive function, can disturb the neuroergonomic driver/vehicle dyad.

Although reliable, widely used screening tools are currently not available, there is some optimism regarding eventual use of road-side, clinic-based, or in-vehicle screening tools for detection of impairments in driver vigilance. There is also a relative lack of large-scale epidemiologic studies examining contribution of various medical illnesses affecting fitness-to-drive although, in this review, some relevant findings of the 2004 Monash Accident Research Centre Report on this topic are highlighted.

As shifts in commercial and personal transportation patterns continue to evolve around the world, strategies for prevention of fatalities and injuries should be developed. Given the wide array of health conditions that may interfere with driving safety, preventative campaigns should focus on *screening* based on functional impairment (as opposed to specific diagnosis), *education* of the public as well specific targeted cohorts (e.g. commercial truck drivers, young novice drivers, elderly drivers) and *skills training*, which may include rehabilitative efforts in certain conditions (e.g. mild disorders affecting the central nervous system). As well, it is important to promote public awareness among non-commercial drivers about the known crash risks and effective management for particular medical conditions or impairments, including those pertaining to pharmacologic treatments.

Road safety and human health: global perspective on a "silent epidemic"

Road safety has emerged as a major public health and preventative medicine challenge of the twenty-first century. The World Health Organization (WHO) World Report on Road Traffic Injury Prevention estimates that 1.2 million people are killed in road traffic crashes each year and up to 50 million more are injured or disabled [1, 2]. According to WHO estimates, without appropriate action, by 2020 road traffic injuries are expected to rise from their current ranking of ninth to third with respect to contributing to the global burden of disease. Projections of future traffic fatalities suggest that the global road death toll will grow by approximately 66% over the next twenty years. This estimate, however, reflects divergent rates of change in different parts of the world; the road death rate is projected to decline by close to 30% to less than 1 per 10,000 in high-income countries, and rise to approximately 2 per 10,000 persons in developing countries by 2020 (with an expected rise in fatalities of close to 92% in China and 147% in India) [3]. Factors playing a role in this trend include an exponential growth of motorized traffic density in driving environments

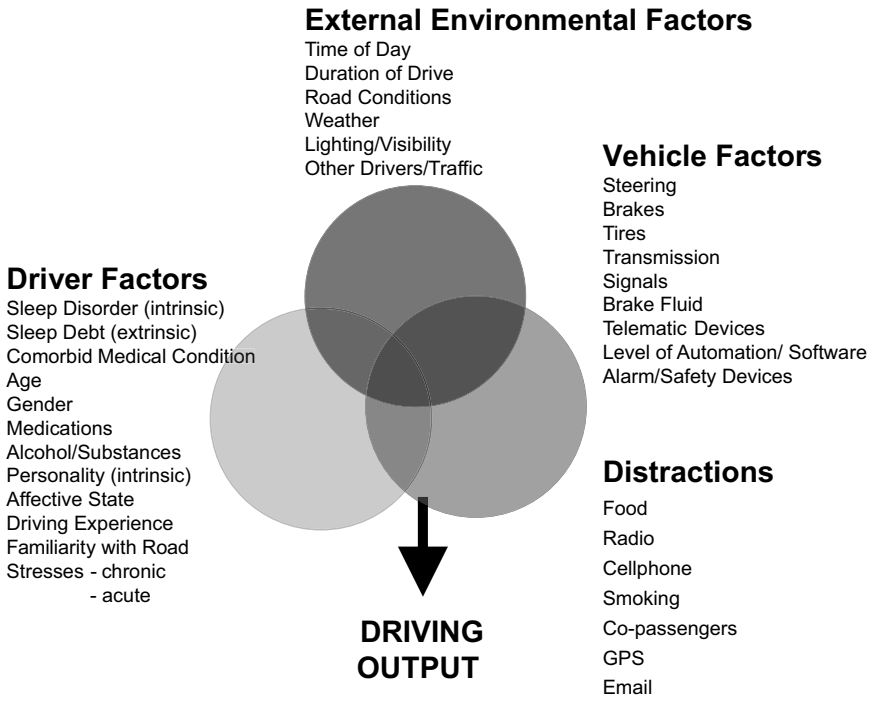

Figure 1 In a Cybernetic Model of Driving Performance, driver health is a complex multifactorial component of traffic safety, and must be considered in the context of vehicle and environment.

lacking safe road design, differential access to timely medical care for traffic injuries, lack of education and enforcement of safety regulations, and a public culture in many countries that does not specifically highlight personal and collective responsibility for safety. Of note, "vulnerable road users" in developing countries are typically pedestrians, bicyclists and motorcyclists, competing for shared road-space with motorized vehicles [2]. With a body of converging research from the fields of medicine, psychology, human factors and road engineering, lessons learned from the field of traffic safety in the developed world may well be extrapolated to prevent a spike of unnecessary morbidity and mortality in regions developing traffic safety programs in coming years.

Once one considers traffic safety from a public health as opposed to transportation perspective, the term "accident" is no longer considered acceptable [4], as explanations are sought to engage in injury prevention as opposed to treatment of morbidity and mortality [5]. A significant issue for consideration in road safety is the impact of medical conditions, including drugs used to treat these, on crash involvement and risk of injury. Medical status of the driver is a key component in a cybernetic model of driving outcome (see Fig. 1), and the influence of prescribed and over-the-counter drugs used to treat medical conditions, as well as alcohol and illicit substances may be considered important subcomponents of driver health.

Ergonomic factors and current sociomedical trends in driver health

Ergonomics, also known as the science of human factors, concerns itself with how human capabilities interface with specific demands, be they work-, task-, or product-related; the goal of applied ergonomics is to maximize operator productivity and safety by reducing discomfort and fatigue. On an ergonomic level, medical traffic safety research therefore seeks to study not only a health condition but also its interrelationship with a specific human-machine interaction dyad, and the wider sociotechnical system this dyad operates in. For many drivers with medical illnesses, the *overall* impact of the condition itself on driving abilities is difficult to quantify, as one must consider the *direct* impact of this condition in addition to the level of knowledge and insight into how the condition and its treatment may impact driving capacity. This may include ability to self-manage symptoms, adherence to physician-recommended treatment and ability to adapt or modify driving activities to improve driving safety.

In his classic neuroergonomic model of human control and behaviour, Rasmussen [6] proposed that during training of a task such as driving, control moves from a knowledge or rule-based level towards a skill-based level, resulting in the reduction in mental/cognitive workload required for the operations involved in the driving task and, thereby, inherently accommodating a larger amount of available attention that can be allocated to other tasks or operations. Depending on the nature of a medical condition, driving capacity can therefore be affected at any of these operational levels, but with appropriate insight or training, a driver may be able to compensate or adapt to a deficit. Driving as a neuroergonomic task involves a complex and continually changing flow of information processing, perceptual and

motor skills, requiring a variety of cognitive and psychomotor performance abilities related to driver health to be intact: alertness, attention, multitasking, memory, co-ordination and visuospatial perception are among the more important. Numerous drugs have the potential to affect any combination of these faculties. Traffic injuries are an often-overlooked cause of potential iatrogenic behavioural toxicities of medications, and in this sense, medical conditions should be considered as both a cause and potential outcome of injury. An integrated approach to traffic safety as a public health problem includes ergonomic issues of driver wellbeing in a broader context that includes risk assessment, health education, technical and environmental prevention, health surveillance and clinical interventions (encompassing timely diagnosis, acute care and rehabilitation of injuries) [7]. As will be discussed, appreciation of the importance of driver health therefore spans the full spectrum ranging from those conditions posing potential risk to those creating a handicap, disability or exclusion to transport safety.

Driver health is as much a challenge to transportation officials and policy-makers on a public level as it is a medical and medicolegal issue for the treating physician. Governmental licensing authorities are faced with the need to formulate policy to manage road safety within their jurisdiction. The challenge for licensing policy is to determine the margin of acceptable risk while balancing the societal and individual need for driving mobility. Historically, there is abundant scientific literature regarding the most important risk factors for road accidents, such as drinking and drug abuse, risk-taking and speeding; however, in the past these have rarely been considered in the context of enduring medical conditions. The more recent targeting of drowsy, fatigued and inattentive driving as the next public health frontiers beyond drinking and seatbelt non-use indicates a possible trend to highlight driver *health,* as opposed to driver *behaviour* as a preventative medicine issue with respect to traffic safety [8]. Reasons for this include a growing awareness of sleep disorders and psychiatric illnesses as conditions with a medical basis that may be modified by environmental conditions and behavioral changes such as day-night schedule, time-on-task and health trends in a 24-hour society [9]. Driver fatigue and drowsiness are now increasingly viewed as conditions that may warrant medical assessment and treatment, particularly in the commercial sector [10]. Driver inattention, particularly in young novice drivers, has been attributed by some authors to attention deficit disorder (ADD) [11]; however, of increasing significance is the interface of the biology of driver attention with the competing demands of distracting telematic and personal handheld devices such as cell-phones, text-messaging, global positioning systems (GPS), and MP3 players on information-processing capacity [12]. The "graying" of the population in developed countries has highlighted fitness-to-drive relative to health status of the aging driver and specifically, progressive dementia has emerged as a societal challenge [13]. Other more clearly defined conditions such as stroke, myocardial infarcts, and diabetes mellitus impose varying restrictions on driving across jurisdictions, and without well-defined guidelines or objective and reliable testing standards, it may be difficult for a physician or licensing body to determine risk on a case by case basis. A recent 5-year

retrospective review by Redelmeier et al. of crashes admitted to an urban Canadian trauma unit investigated three chronic medical conditions (alcohol abuse, cardiac disease and neurological disorders) [14]. While 85 % of these individuals had seen a physician within the past year, only 3 % had been reported to licensing authorities despite an exceedingly over-inclusive legal obligation to report "any condition which may make driving dangerous". This study highlighted (1) that unsafe drivers often visit physicians but (2) rarely seek medical care specifically to undergo driving assessment, and (3) are rarely reported to licensing authorities even when mandatory reporting laws are in place. The usefulness of similar laws and guidelines appears questionable if they are largely ignored by clinicians, implying a potential need to rethink shared responsibility for traffic safety among involved stakeholders. At present, evidence-based decision-making regarding driver health apparently remains an oftentimes-uncomfortable ethical dilemma weighing individual access to mobility and its attendant quality-of-life, socioeconomic and health benefits versus the safety and health of the public.

The Monash Accident Research Centre Report

As discussed, health conditions may have a variety of functional consequences on activities such as driving, and attempting to disentangle the societal as well as statistically acceptable risk has presented much confusion to policymakers and licensing authorities. One of the most comprehensive reports regarding the influence of chronic medical conditions on traffic safety was published in 2004 by the Monash University Accident Research Centre in Melbourne, Australia [15]. The aim of this ambitious project, sponsored by the Swedish National Road Association, was to review the evidence for the influence of chronic illness and impairments on crash involvement of motor vehicle drivers. The Monash Report assessed the current state of knowledge relating to the magnitude of this problem in developed countries, taking into account the prevalence of specific medical conditions and the evidence for crash involvement and other measures of driver risk. The study noted a fairly wide variety of guidelines and recommendations for risk management across jurisdictions and licensing authorities, and frequently, inconsistencies in light of apparent evidence for crash risk. A relative risk rating system was applied to the available evidence on crash risk for all medical conditions studied, in order to identify those conditions that presented greatest risk. The overall risk for each condition was rated as "higher", "not different" or "inconclusive" compared with relevant control groups. Three levels of ratings for "higher" risk conditions were applied: *slightly high*: (RR: 1.1–2.0), *moderately high*: (RR: 2.1–5.0) and *considerably high*: (RR: 5.0+), with information on post-treatment risk also considered in the relative risk ratio. These risk assessment levels were primarily based on studies examining crash involvement, although epidemiologic studies investigating risk on the basis of driving citations and experimental studies investigating either on-road or simulated driving performance were also considered.

Table 1 Crash risk associated with high-risk medical condition.

Condition	Prevalence (Population-based) %	Overall Crash Risk	Post-Treatment Crash Risk
Alcohol Abuse and Dependence	Alcohol abuse: 3%, dependence 4%	Slightly to moderately high	Inconclusive
Dementia	2–3%	Moderately high	Inconclusive
Epilepsy	1%	Slightly to considerably high	Inconclusive
Multiple Sclerosis	0.05–0.06%	Moderately high	Inconclusive
Psychiatric disorders (as a group)	25% (at some time during life; includes substance abuse)	Slightly to moderately high	Benzodiazepines – Higher compared with controls without the condition (Methodological problems prevent the separation of risk associated with drug vs. condition). Tricyclic antidepressants – Higher compared with controls without the condition (Methodological problems prevent the separation of risk associated with drug vs. condition).
Schizophrenia	1–2%	Moderately high	Inconclusive
Sleep apnea	0.3–4%	Moderately to considerably high	CPAP – Lower compared to controls without sleep apnea
Cataracts	2–3% (40–50yr olds)	Moderately high	Cataract surgery – Lower compared with untreated cataract; – Inconclusive compared with those without the condition

* (as reported in *Monash Accident Research Centre Report* (2004) [15])

A limited number of conditions were found to have at least a moderately elevated risk of crash involvement in comparison to controls. These were psychiatric disorders (as a total group, and schizophrenia specifically), alcohol abuse and dependence, sleep apnea, dementia, epilepsy, multiple sclerosis, and cataracts (see Table 1). The study highlighted the current state of relative uncertainty of the scientific literature regarding medical conditions affecting driver health: with respect to methodological validity of the current body of available research on medical conditions affecting crash risk, no studies were found which used population-based, prospective designs. Generally, the best studies reviewed used retrospective, case-control design with adequate sample size, reliable diagnosis of health condition and valid measures of crash involvement. However, most studies were found to have some degree of bias, such as lack of control for driving exposure, and heterogeneity of disorder type, severity and duration. The clinical reality of co-morbidity in multiple medical conditions increasing the complexity of risk prediction was stressed in addition to the concept of *functional* impairment. The Monash report highlighted the need for a cooperative international approach to future research using population-based, prospective studies to advance scientific knowledge and public policy linking medical conditions and crash risk.

Disorders of mental function and driving safety

As with other aspects of behavior, impaired driving in mental disorders may be seen through the lens of the "Mad versus Bad" dilemma in psychiatric diagnosis, depending on the theoretical paradigm used [16]. Psychiatrically ill individuals have often been stereotyped as dangerous drivers, sometimes without serious epidemiological basis, when total distance driven (i.e. cumulative risk exposure) and co-existing use of alcohol or psychotropic drugs is controlled for [17, 18]. Nevertheless, potential areas of functional/neuroergonomic impairment correlating with psychiatric disorders include [15]:

- impaired information-processing ability, i.e. attention, concentration, and memory components
- reduced sustained attention, (i.e., alertness/vigilance);
- impaired visuospatial functioning;
- increased psychomotor response latency;
- impaired impulse control, including increased risk-taking in some disorders;
- poor judgment and problem-solving, including the ability to predict/anticipate;
- diminished ability to perform under more complex, distracting and stimulus-rich conditions, particularly in a crisis context.

As the nature of psychiatric illnesses typically involves state-dependent fluctuations in functional impairment, their precise effect on driving ability may be unclear. This is an issue of particular significance in jurisdictions mandating duty-to-report by physicians and other health-care providers [19, 20]. In a 2006 Canadian survey of

248 psychiatrists, the majority (64.1 %) responded that they considered the issue of addressing patients' fitness to drive an important issue [21]. However, only 18.0 % of psychiatrists were always aware of whether their patients were active drivers and only 25 % of respondents felt that they were confident in their ability to evaluate fitness to drive. The authors concluded that a knowledge gap and need for education about evidence-based fitness to drive exists among psychiatrists.

The interface of psychiatric illnesses and potentially performance-impairing (or enhancing) effects of drugs used to treat these is, of course, a complex one. An example of this is the widely used marker of weaving tendency (or increased standard deviation of lane position- SDLP) in simulator and on-road tests to assess potential effects of antidepressants on driving. It is counterintuitive that depression alone produces impairment patterns of increased weaving tendency similar to alcohol, except when accompanied by hypersomnolence. Thus, lane deviation (weaving) patterns may be useful to assess sedating effects of psychotropics, but less so for the neurocognitive deficits related to the illness itself [22], which might affect reaction time, particularly in the face of sudden unpredictable events. Depression and other mood disorders have been demonstrated to potentially elevate crash risk due to diminished psychomotor responsiveness [24]. Tricyclic antidepressants and benzodiazepines are thought to elevate crash risk beyond that of illness itself, while most novel antidepressants are believed relatively benign or even "performance-enhancing" [23], when one considers risk ratio of treated versus untreated illness; nevertheless, caution must be exercised upon instituting pharmacological treatment, and even once a steady-state is reached, individual variations and idiosyncratic drug reactions need to be considered.

Schizophrenia is an illness with a prevalence of 1 % across cultures, and was estimated by the Monash report as imposing a moderately elevated crash risk, although the report is inconclusive with respect to fitness-to-drive in patients treated with antipsychotics. Complicating this is the drastic symptom fluctuation between acute psychotic versus residual illness states. Further, functional status with respect to independent activities such as driving has been found to have an inverse relationship with negative symptoms [24], suggesting that preserved driving ability may be an independent predictor of functional outcome in schizophrenia worth targeting therapeutically. Brunnauer et al., who undertook the largest published controlled study of acutely ill psychotic patients treated with neuroleptics [25], argue that psychomotor functions of most schizophrenic patients partly remitted should be considered as being impaired, even when stabilized on treatment. While periodic neuropsychological examination of such patients can be useful to predict fitness to drive, these tests, even when involving simulated driving exercises, rarely are able to accurately discriminate performance under stochastic or high-stress conditions.

Public health officials and the insurance industry have long been aware of the elevated incidence of traffic incidents in young novice drivers, particularly young males, an epidemiologic cohort where adult ADD is most likely to be diagnosed [26–30]. This does not necessarily imply, however, that ADD itself is the chief cause of this elevated crash risk. Young drivers, whether "normal" or attention-

disordered, are also most likely to be users of distracting telematic devices. As Lee points out, "infotainment" technology stresses the same vulnerabilities that already lead young drivers to crash more frequently than other drivers, without the specific diagnosis of ADD [30]. Cell phones, text messaging, MP3 players, and other portable media devices all present a threat because young drivers may lack the spare attentional capacity for vehicle control and the ability to anticipate and manage hazards. Fischer et al. have recently suggested a possible causal relationship between frequent participation in immersive car-racing video games and subsequent on-road risk-taking behaviours in teens and young adults [31], a phenomenon perhaps best described as videohypertransference.from simulated to real-world behaviours [32]. Aside from neurocognitve models of ADD, this may relate in general to relatively immature frontal lobe control in adolescents [33].

It remains to be rigorously demonstrated that ADD drivers, compared to same-age peers, are particularly prone to misuse infotainment devices, and if so, whether treatment with medication or skills-management and educational training with respect to safe driving performance is likely to be of greater benefit. Improved knowledge of effects of acute and prolonged treatment with medicines such as stimulants that affect attentional processes would be desirable. Specifically, beneficial effects on potentially lowering crash risk in clinically diagnosable ADD must be weighed against effects on sleep as well as risk of misuse, both in terms of illicit recreational use and inappropriate self-medication of fatigue states in young drivers and commercial vehicle operators [34, 35]. Gaining a clearer understanding of the underlying processes, both physiologic and behavioural, correlating with increased crash risk in young drivers remains an important component of preventive health campaigns.

As will be discussed in the next section, an important confounder is the effect of sleep disturbance on mental function and illness; hypersomnolence or insomnia may both be features of psychiatric illness. While increased daytime somnolence

Table 2 The spectrum of high-risk scenarios for collisions due to driver impairment varies from Type 1 (underarousal/drowsiness) to Type 2 (overarousal/cognitive overload).

Type I	**Type II**
Single vehicle	Multi-vehicle
Lack of external stimulation	Overstimulation results when mental tasks excessively complex and sustained
Boredom/underarousal, leads to lowering of brain activity	Multi-tasking/overarousal
Rural/ Long monotonous stretch of highway	Urban/suburban intersection
Circadian component	More often related to traffic volume

typically presents a higher "Type 1" crash risk in a single-vehicle context, particularly if there is a circadian tendency towards sleep-proneness or sedating psychotropics are involved, insomnia patients more typically demonstrate fatigue and reduced vigilance without frank sleepiness [36]. Such patients may be more prone to demonstrate a risk in "Type 2" traffic situations requiring intensive mental workload, rapid shifts in cognitive set and decision-making [37]. An ideal simulator or on-road global assessment battery for driving impairment related to mental function affected by the spectrum ranging from drowsiness to high-stress "overload" states might therefore possess components of both "Type 1" (underarousal) and "Type 2" (overarousal) scenarios, including introduction of hazards and challenges.

Sleep health and driving safety

Traffic injuries and fatalities due to sleep loss and sleep disorders are a growing public health burden. The most recent American National Highway Traffic Safety Administration report suggests that drowsy and fatigued driving is the next public health awareness frontier beyond drunk driving and seatbelt non-use [38]. The specific issue of young road users as vulnerable to crash risk is now recognized by organizations such as the WHO [1], however, most emphasis remains on risk-taking behavior, speeding and drunk driving, with a relative failure to include sleep-related risk factors. The relationship between distracted and drowsy driving also needs to be clarified. These are typically classified as independent risk entities by public health and transport agencies, when in fact, current research suggests a complex relationship between disturbances in sleep and alertness-requiring tasks [39–41].

Obstructive sleep apnea (OSAS) is a common syndrome, affecting between 3 to 7% of adults in Western countries, especially over-weight males older than age 40 [42]. OSAS is most typically caused by recurrent episodes of upper airway obstruction during sleep; this results in sleep fragmentation and hypoxia. One of the major comorbidities of OSA is obesity in children as well as in adults. Other contributing factors include retrognathia, macroglossia, nasal obstruction, older age and use of central nervous system (CNS) depressants causing pharyngeal muscle relaxation [43, 44]. Treatment of OSAS using continuous positive airway pressure (CPAP) has been shown to reduce crash risk to the same level as that of drivers without the condition [45].

Other common sleep disorders relevant to driving include chronic insomnia, narcolepsy, idiopathic hypersomnia, restless legs syndrome (RLS) and periodic limb movements in sleep (PLMS). Moller et al. differentiated subjective impairment due to sleepiness from impaired alertness in four different sleep disorders (OSAS, chronic insomnia, periodic limb movements in sleep and narcolepsy), finding that while OSAS and narcolepsy patients were significantly more sleepy patients, all four groups suffered from near-equivalent degrees of impaired of alertness [36]. Aldrich et al. performed a retrospective analysis of crashes in 70 healthy

subjects and 424 clinically diagnosed patients with OSAS, narcolepsy, and other disorders of excessive sleepiness, as well as sleep disorders without excessive sleepiness, such as insomnia and PLMS. The relative risk for sleep-related crashes was 1.5–4 times greater in the somnolent patient groups than in the control group. In patients with hypersomnia (due to conditions such as OSAS and narcolepsy), the incidence of sleep-related crashes per year of excessive sleepiness was 3–7 % [46]. Chronic insomnia (lasting for more than one month) is estimated to exist in about 10 %–15 % of adults [47–49], and can be associated with a variety of medical and psychological comorbidities. Reduced alertness and increased fatigue are common daytime consequences with implications on fitness to drive [50], and a recent French occupational health survey of 738 blue- and white-collar workers found a 3-fold increase in self-reported serious car crashes for subjects with insomnia [51]. The risk-benefit ratio of sedative-hypnotics versus the alertness-impairing effects of sleep disruption itself must be considered both on an individual and economic basis [52].

Possibly the most important preventable sleep-related cause of automobile collisions, however, may be behavioural, (i.e. self-imposed sleep loss) as opposed to medical. (i.e. diagnosable sleep disorders), and the manifestations on driving performance can be quite varied. Interrelationships between driver sleepiness, fatigue and inattention remain poorly understood: crashes due to drowsiness and distraction are often stratified as separate entities by researchers in the safety and transport sectors [8, 53]. Young male drivers in particular have been identified to have an increased rate of motor vehicle crashes [54], however to date, far more emphasis has been placed in major public health reports on risk-taking behaviors other than self-imposed sleep loss. As traffic density continues to grow in an increasingly interconnected and 24-hour society, more drivers will be transiting in high-density traffic both day and night [9, 55]. Traditional human factor risk models of sleep-related crashes will need to accommodate changes in work and traffic patterns that might interact with human circadian biology of sleep requirements. One example of this trend has been the inclusion of shift-work sleep disorder in the ICD-9 and DSM-IV to describe individuals who display “unnatural” excessive sleepiness or insomnia as a function of their shift work, with a 10 % estimated prevalence [56].

It is established that sleep-related crashes will occur in single-vehicle monotonous rural scenarios during the early morning sleepiness nadir [57], but it remains to be clarified whether driving safety in more complex urban environments requiring set-shifts and cognitive strategizing is equally affected by fatigue and sleep loss. Individuals who are deprived of sleep have been shown not only to be drowsy, but also to have reduced sustained attention, slower reaction time (RT), poorer judgment capacity, decision-making skills, working memory and concentration [58]. Inattention and deficits in alertness while driving may represent sub-threshold risk states that are not recognized as “falling asleep”, but may be either a precursor or variant of frank somnolence, modified by arousal state and an individual’s vulnerability in cognitive reserve [36].

Aging, dementia and traffic safety

The population of developed countries is becoming increasingly elderly and, concurrently, the prevalence of dementia is rising steadily. The natural processes of aging and senescence are associated with changes in cognitive, sensory and motor function, and chronic health-related conditions become most prevalent in older age groups. In healthy aging, compensatory efforts incorporated by the driver at the strategic level (planning when and where to drive) and tactical level (driving more slowly or cautiously) are used to offset changes in biological function. Of all age groups, those over 65 years of age have the highest crash rate per kilometer driven [59]. The issue of driving in the elderly as a group must be separated from that of elderly with health conditions, ranging from "benign" conditions such as insomnia to progressive dementia, where the ability to drive safely is eventually lost [60]. For this reason, routine screening of driving safety is commonly an "illness-unbiased" and age-dependent procedure of most developed countries' licensing authorities.

Dementia occurs through a progressive loss of memory and cognitive function due to CNS atrophy, usually with an additional impairment in one of the following: aphasia, apraxia, agnosia or disturbance in executive functioning [15]. More common types of dementia include Alzheimer's type, vascular dementia, frontotemporal dementia, or a Lewy body dementia variant of a Parkinsonian disorder. Prevalence of dementia in developed countries is estimated at 8% for those over 65, increasing to 30% for those over 90 years old [59]. The most common types of serious crashes in drivers with dementia are rear-end collisions. Uc et al. have studied drivers with advanced Alzheimer's [61] and Parkinson's dementia [62] using a high-fidelity driving simulator paradigm and found measures of visual perception, attention, visuospatial abilities, memory, and executive functions to correlate with these types of crashes. Neuropsychiatric symptoms such as agitation, apathy and hallucinations also appear to be clinical predictors of driving cessation in dementia patients [63].

Nevertheless, many individuals with mild dementia remain capable of driving safely, if they are able to appropriately employ the same compensatory strategies as their healthy same-aged peers. The desire for an individual to continue to drive even after the diagnosis of dementia is given is understandable on a humanitarian/social level. Stopping driving can limit access to family, friends, and services and is an independent risk factor for entry to a nursing home [64]. A recent commentary by O'Neill highlights the point that any public health discourse related to limiting driving for the elderly include outdoor mobility and transportation options for our patients [65].

Other disorders of the central nervous system affecting driver health

Further neurological conditions flagged in the Monash report as imparting a statistically elevated crash risk include epilepsy and multiple sclerosis. Epilepsy is a

heterogeneous CNS condition both in terms of etiology and functional impairment *vis-à-vis* driving [66]. Seizure-free intervals, the presence of auras to predict epileptic attacks and the use of antiepileptic drugs are among the factors that need to be considered in individual decision-making regarding driving privileges. While differential effect of anticonvulsants on cognitive function has been reviewed [67], limited research exists comparing impact of various anticonvulsants specifically on driving ability. Syncope is a disorder of disturbed consciousness sometimes confused with seizure-like events that may be occur secondary to CNS, cardiovascular, otologic or pharmacologic causes. It is typically differentiated from epilepsy by benign EEG findings, although mixed syncopal/epileptiform episodes may occur in some individuals. Assessment typically includes cardiac monitoring and evaluation of potential pharmacologic contribution.

Multiple sclerosis (MS) is an incurable, autoimmune, chronic and often progressive demyelinating disease of the CNS; it one of the most frequent causes of neurologic impairment in early to middle adulthood, and in the Monash report was thought to impart a moderately elevated crash risk [15]. Worldwide prevalence of MS is approximately 2.3 million, with females affected more commonly than males, by a 2:1 ratio; prevalence is thought to lie at 0.05 percent of the population, with an uneven geographic and ethnic prevalence distribution [68]. Individuals affected by MS may demonstrate widespread, multifaceted impairments in many domains of physical and cognitive function [69]. While sensorimotor symptoms such as transient visual disturbances, spasticity, motor dyscoordination or tremor may significantly affect function, cognitive impairments resulting from MS are thought to impose the greatest risk of driving impairment [70]; analogous to older drivers with mild dementia, drivers with MS may drive less than healthy individuals because of self-regulation or as a consequence of decreased occupational activity.

Neuropsychiatric symptoms such as mood disturbance and fatigue related to CNS involvement may overlap with neurocognitive symptoms that closely mimic similar impairments found in primary psychiatric disorders. Decreased attentional and visual perceptual skills, slowed information processing speed, and executive dysfunction are thought to most significantly affect driving performance. Lincoln has shown predictive validity of 88 % between performance on a battery of neuropsychology tests (including Stroop, paced auditory serial addition test and information processing battery) and on-road assessment ("safe" versus "unsafe") by an instructor blind to a subject's clinical status [70]. Patient function between, during and after episodes varies significantly and, unlike epilepsy, the array of classes of pharmacological agents used to treat MS is wide, including steroids, disease-modifying agents, antidepressants, stimulants and antispasmodics, with no definitive studies in existence examining driving risks specific to these treatments [15]. This makes unbiased evaluation of functional status with respect to neurocognitve functioning particularly important in assessment of fitness to drive.

While not specifically defined as conditions imparting an increased risk of driving impairment by the Monash report, traumatic brain injury (TBI) and stroke are other important CNS causes of functional morbidity related to fitness-to-drive. The WHO classification of mild, moderate and severe traumatic brain injury is widely used in stratifying patients in the sub-acute or chronic phase of their clinical trajec-

tory, assisting in rehabilitative care and medicolegal communication [71]. Post-concussion syndrome, a specific variant of mild traumatic brain injury, is notable for its controversy and prevalence. Patients with this neurological syndrome frequently endorse a wide range of symptoms, many of them subjective. Specific validity tests such as the Word Memory Test have been developed to evaluate neurocognitive effort, thought by some authors to be more relevant to functional impairment in effort than effects of the TBI [72].

A common, related health consequence for drivers following motor vehicle collisions involves the development of complex fear responses, including post-traumatic stress disorder (PTSD), with symptoms often difficult to discern from neurological injury due to TBI. Driving phobias may be so severe that individuals are limited to driving very short distances or, in some cases, they may be unable to drive at all. In any given year, approximately 1 % of the American population will be injured in a collision [73] and between 20 to 40 % of crash survivors develop PTSD [74], with 11 % continuing to meet criteria at 3-year follow-up [75]. Unless the key fear of re-engaging in an accident is addressed and desensitized with emotional processing, the crash survivor with PTSD-related driving phobias remains at high risk of developing a recurrence or relapse with further collisions [76]. If an individual avoids driving situations for prolonged periods, routine-driving skills previously learned begin to deteriorate, causing secondary deconditioning of psychomotor skills. Simulation practice allows treatment to occur in the privacy of a clinic or laboratory setting, and involves graded exposure behavioral treatment models of anxiety and phobic responses, typically using a combination of standardized and individualized protocols [76, 77]. In a simulator-training model, graded exposure therapy for driving-related anxiety overlaps with psychomotor skills training/retraining. A course of simulator-based therapy can therefore either serve as a segue to on-road assisted driving retraining or be used as stand-alone therapy leading to autonomous driving [77, 78].

Evaluation of driving ability may include consideration of assistive devices and psychomotor rehabilitation training exercises. Promising developments in this area include the use of simulated and virtual-reality exercises to retrain neurocognitive function in a context that is meaningful to the patient, while allowing a safe and scientifically rigorous evaluation environment of driving skills that is transferrable to “real-world” driving environments [77, 78]. Akinwuntan et al. recently demonstrated significant benefit in on- as well as off-road driving assessments at six to nine months post-stroke in a randomized controlled trial of 83 subjects with subacute stroke predominantly affecting neurocognitive (as opposed to motor) function [79]. The trial involved a 5-week 15-hour driving simulator training program versus training of cognitive tasks related to driving but without a driving simulator. While both groups made gains on visuospatial and a variety of neuropsychological functions, the simulated environment with ecological similarity to real-world driving performance was hypothesized to enhance skills specific to driving.

Aside from skills training, virtual reality driving environment training may also offer transfer of training related to the real-life use of mobility devices [78]. While it remains somewhat controversial how high the fidelity of simulation needs to be to screen for driving impairments in various CNS disorders, simulators clearly offer

an unbiased assessment of psychomotor performance related to functional impairment across diagnoses and including the variety of medicines and drugs that can affect performance.

Vision disorders affecting traffic safety

Unlike most other aspects of driver health, vision disorders represent one group of medical conditions that have a more established history of being recognized as impacting driving safety. Aside from cognition, intact visual function is arguably the most important aspect of driver health, with some researchers estimating vision to be responsible for 90 or 95 percent of sensory input for drivers [80]. Visual acuity screening has been a routine component of licensing renewal for older adults in many jurisdictions, although methodological heterogeneity in different parts of the world makes a global assessment of effectiveness of these screening interventions to reduce vision-specific relative crash risk difficult. Visual acuity, visual field, depth perception, contrast sensitivity, colour vision and glare recovery during night driving are among the most important functions that can be affected by medical conditions. In many medical conditions, crash risk is likely to be attributed to more than one aspect of visual functioning. For example, neurodegenerative conditions such as Alzheimer's or Parkinson's disease are associated with impairments in visual acuity, contrast sensitivity, color discrimination, temporal sensitivity, motion perception, peripheral visual field sensitivity, and visual processing speed [81]. The most common sight-threatening conditions in the developed world are cataract, age-related maculopathy, glaucoma, and diabetic retinopathy [82, 83]. Even in their moderate stages, these conditions cause visual impairments and affect instrumental activities of daily living such as driving. The most common deficit, refractive error causing reduced acuity, may be readily and affordably corrected. However, in many cases some visual deterioration will have occurred and the individual affected by the condition may continue to drive, potentially increasing crash risk.

Cataracts are the leading cause of blindness globally and among vision disorders were specifically identified in the Monash report as imparting a moderately high relative risk of crash, which normalizes with surgical treatment [15]. While prevalence in middle age is estimated at 2 to 3 %, cataracts are common in the geriatric population across cultures, with an estimated prevalence of half of all adults over 75 found in a North American study by Klein et al. [83]. They are highly treatable, although surgery is typically delayed until there is significant reduction in visual function, implying that older drivers with compromised vision due to cataracts are likely a common potential hazard to public safety. Visual loss associated with the other three prevalent conditions can usually be managed medically if detected early enough, but may also be potential sources of driving impairment.

When minor visual defects are not accompanied by cognitive defects, drivers are typically able to compensate; most otherwise healthy drivers, for example, are able to eventually adapt to monocular vision [84]. In the presence of even mildly impaired visual function, however, a driver's compensatory capacity is more likely

to be compromised. This implies that vision standards need be considered in the context of overall functional capacity, and in fact visual acuity testing is one of the more commonly performed screening procedures in elderly drivers. Another important concept related to functional impairment is useful field of view (UFOV), describing the area from which useful visual information can be extracted in a single glance. Visual function and health must be considered not only in the context of medical disorders, but also in terms of phenomena such as cognitive loading; UFOV has been shown to be significantly affected by direct visual impairments such as central scotomas [85], as well as by mental impairments such as temporary cognitive impairment while using mobile phones (be they hand-held or hands-free) [86]. Reduced UFOV in young healthy drivers with normal visual function using mobile phones or conversing with passengers has been shown to cause low-to moderate elevation in crash risk [87], and this tendency is likely exacerbated in older drivers and those with cognitive impairments. With respect to drugs that might affect driving performance, the role of the visual system as a vital component of cognition should also be taken into consideration. As with cognitive impairment, consideration should be given to the correlation of loss of vision with ability to appropriately adhere to medication regimens that may affect overall health and fitness to drive [88].

Conclusion: Disentangling causes and finding preventative solutions

In this chapter, traffic safety has been described from a medical and epidemiologic model, including data regarding current knowledge regarding several specific conditions. Driver health and traffic safety is clearly an evolving and multidisciplinary area of research and development. The notion of transport safety being viewed as a public health issue is still relatively novel, and represents a current convergence of human factors, medicine and psychology research. To better characterize risk related to specific medical conditions, large-scale prospective epidemiologic studies would be useful, particularly for health- and safety-related public policy. As a counterpoint to this, the rapidly changing landscape of road usage, and consequent to this, crash trends in many parts of the world have the potential to quickly outdate studies.

The art and science of medicine have been described as a stochastic process [89], and this analogy lends itself well to preventative interventions relating to traffic safety. While a physician may perfectly perform his or her craft, a patient may nevertheless die from an illness due to difficult to control variables. While a deterministic model of medical conditions affecting driving safety would be desirable, the cybernetic model of multiple factors interacting with driver health (see Fig. 1) illustrates that it is extremely difficult to control for innumerable extraneous fac-

tors interfacing with medical states. Thus, on an individual level, driving safety is a stochastic, continually changing and non-deterministic process. Experimental investigation related to driver health and disease affected by drugs used to treat these is one area of research with the potential to add certainty to complex models of risk assessment to improve public safety.

A medicalised approach to traffic safety is a public health frontier with very significant future socioeconomic and healthcare implications. Authoritative epidemiological studies such as the Monash Report are extremely useful in delineating relative risk ratios specific to different medical conditions. However, the reality of comorbidities, both medical and behavioural, challenge researchers of traffic safety to be aware interconnections between conditions, including pharmacological implications.

As shifts in commercial and personal transportation patterns continue to evolve around the world, strategies for prevention of fatalities and injuries should be developed. Given the wide array of health conditions that may interfere with driving safety, preventative campaigns should focus on *screening* based on functional impairment (as opposed to specific diagnosis), *education* of the public as well specific targeted cohorts (e.g. commercial truck drivers, young novice drivers, elderly drivers) and *skills training*, which may include rehabilitative efforts in certain conditions (e.g. individual with mild CNS disorders, or requiring assistive aids to augment driving ability). As well, it is important to promote public awareness among non-commercial drivers about the known crash risks and effective management for particular medical conditions or impairments, including those pertaining to pharmacologic treatments.

Policy related to this medical issue needs to develop realistic approaches regarding reporting of health conditions affecting driving safety, recognizing that universally accepted reliable, evidence-based, ecologically valid tests of fitness-to-drive are not yet in existence. A further controversy is the onus of responsibility regarding driving cessation or restriction. The "graying" of the population in developed countries has highlighted concerns about screening and infrastructure mechanism to accommodate those elderly individuals that become unfit to drive. Young novice (and otherwise healthy) drivers are thought to represent a far more significant threat to public safety on a global scale, however, than the elderly, those with chronic medical conditions or alcohol-impaired drivers as a group [15]. Contributing factors in this group include risk-taking, inexperience, self-imposed sleep loss as well as use of mobile communication and entertainment devices.

Driver health encompasses both physical and psychological wellbeing, and this review has highlighted the role of sleep disturbance as an important intermediary state between mind and body, with drowsy, fatigued and inattentive driving now increasingly recognized as preventable states of impairment comparable to alcohol. Further questions exist: to what extent could risk-taking behavior by a driver be placed on the spectrum of "medical conditions" [31]? What challenges do in-vehicle electronic distractions and increasingly complex road environments play in colliding with limitations of cognitive capacity for information processing allowing

safe driving? A neuroergonomic approach to traffic safety evaluation recognizes that driving is a behavior with multiple layers of complexity, and the sensorimotor car-driver loop may be disrupted through a variety of mechanisms.

The widespread prevalence of automobile drivers with chronic health conditions are a reality related to healthcare advances allowing for longer lives and better functional outcomes, as well as changes in occupational/vocational patterns, with much more mobile and car-reliant societies across the world. It is hoped that improved knowledge in healthcare research gained from emerging evidence relating to particular medical conditions and risk factors will be translated into effective road safety campaigns around the world.

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Worldwide trends in alcohol and drug impaired driving

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Abstract

This chapter summarizes recent trends in a number of industrialized countries around the world and discusses the reasons for the changes that have occurred. It also reviews current programs designed to produce further reductions in impaired driving. In the decade of the 1980s, there were impressive declines in drinking and driving in much of the industrialized world. The declines included about 50% in Great Britain, 28% in Canada and The Netherlands, 32% in Australia, 37% in Germany and 26% in the U.S. These declines did not continue in the early part of the 1990s. In some countries, there were actually increases. Toward the middle and latter part of the decade the increases stabilized and we again began to see some decreases. However, these decreases have been at a slower rate than the dramatic decreases in the 1980s. Toward the end of the 1990s and in the new century, the record has been mixed. Clear trends have emerged. Some countries (France and Germany) continued to reduce drinking and driving while in other countries (Australia, Canada, The Netherlands, Great Britain and the United States), there has been stagnation and in some cases small increases or even a large increase in the proportion of alcohol related fatalities, as was the case in Sweden. Trends on drug impaired driving are also beginning to emerge in some countries. These trends will also be discussed.

Worldwide trends in alcohol impaired driving

in the decade of the 1980s, there were impressive declines in drinking and driving in much of the industrialized world. The declines included about 50% in Great Britain, 28% in Canada and The Netherlands, 32% in Australia, 37% in Germany and 26% in the U.S. Suggested reasons for the declines included improved laws, enhanced enforcement, and public awareness brought about by citizens' concern. Other possible explanations included lifestyle changes, demographic shifts, and

economic conditions. The magnitude and reasons for the worldwide decline varied from country to country [1]. These declines did not continue in the early part of the 1990s. In some countries, there were actually increases [2]. Toward the middle and latter part of the decade the increases stabilized and we again began to see some decreases. However, these decreases have been at a slower rate than the dramatic decreases in the 1980s [3]. Approaching the end of the 1990s and early in the new century, the record has been mixed [4]. In the last few years, some countries (France and Germany) continued to reduce drinking and driving while in other countries (Australia, Canada, the Netherlands, Great Britain and the United States), there has been stagnation and in some cases small increases or even a large increase in the proportion of alcohol related fatalities, as was the case in Sweden [5].

It is important to keep in mind that comparisons among countries are complicated by differing methods in each country of measuring and reporting alcohol involvement in traffic crashes. For example, definitions vary on such basic items as, *fatality, alcohol-involved drivers* and *legal limit.* In addition, the number of drivers in fatal crashes tested for alcohol varies from country to country and it is not possible to know in some cases whether these drivers are representative of drivers in fatal crashes as a whole. While it is not meaningful to compare the record of one country against another, it is useful to examine the trends in each country.

Australia

The percentage of fatally injured drivers and motorcycle riders who had a BAC above the legal limit decreased from 44 percent in 1981 to 30 percent in 1992. (Most of the country had a legal limit of 0.05 % during this period.) There was also a general corresponding decrease in the percentage of drivers found in roadside breath alcohol surveys above 0.08 % from 1979 to 1992. The observed decline in drink driving was accompanied by a decline in alcohol consumption. The quantity of absolute alcohol consumption per person aged 15 years and over decreased by 26 percent from 1981–1983 to 1991. There was a marked change in beer drinking, with low alcohol beer assuming an increasing proportion of beer sales.

The reductions in drinking and driving (through 1992) most likely resulted from a combination of: 1) the widespread use of random breath testing, 2) formal and informal publicity about drink driving and its possible consequences, 3) other factors include the increased use of seat belts (now close to 100 percent), and other vehicle safety measures [6].

Not much progress has occurred since 1992. From 1988 to 1992, alcohol related fatalities declined from 43 % to 35 %. From 1992 to 2003, the percentage was fairly steady, ranging from 35 % to 39 %. The exact number of alcohol related fatalities is not available, as the percentage of alcohol related fatalities noted above is based only on those fatalities where there is a know BAC. Total fatalities dropped from 2887 in 1988 to 1755 in 1998. Since then, the number of fatalities has fluctuated from a high of 1817 in 2000 to a low of 1583 in 2004. There were 1601 fatalities

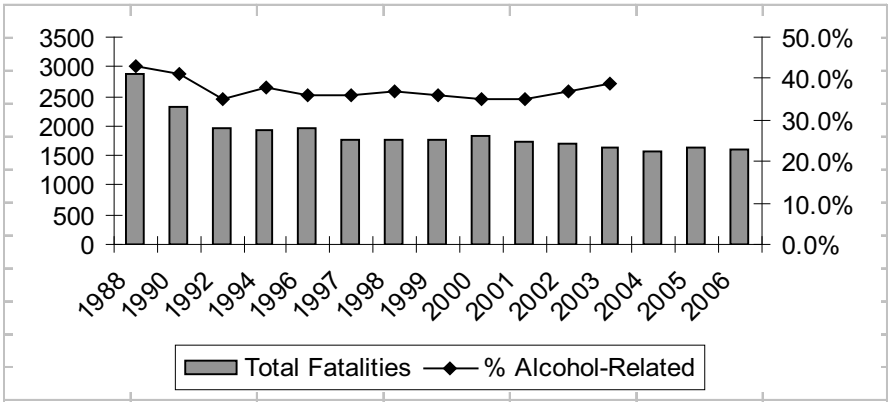

Figure 1 Australia – total fatalities and percent alcohol related (where known). Source: ATSB.

in 2006. Figure 1 shows the total fatalities from 1988 to 2006 and the proportion of alcohol related fatalities, where know, from 1988 to 2001 [7, 8].

The Australian National Road Safety Strategy 2001–2010 provides a framework for coordinating the road safety initiatives of the federal, state, territory and local governments and of others capable of influencing road safety outcomes. The road safety strategy aims to reduce the number of road fatalities per 100 000 population by 40 per cent by 2010. The strategy is supported by the current action plan for 2007–2008. This plan notes that:

– More than one in five drivers and riders killed on Australian roads have a blood alcohol level exceeding the legal limit.
– About four in ten pedestrians killed have a blood alcohol concentration over 0.05 g/100mL and about three quarters of these have a BAC of over 0.15 g/100mL, and the incidence of intoxication is highest among male pedestrians aged between 15 and 54 years.
– Random breath testing results show that on average 1 in 300 drivers tested exceed the legal limit.
– A high proportion of recidivist drink drivers have clinical alcohol dependence problems.

The national road safety action 2007–2008 proposes that, to combat impaired driving in Australia, the major focus should be on maximizing the effectiveness of enforcement and public education to tackle drink driving, particularly in rural areas, for example by improving rural random breath testing (RBT) effectiveness through innovative combinations of general deterrence and targeted operations.

Other initiatives in recent years include responsible service of alcohol programs, and the commencement of alcohol ignition interlock programs and interventions

targeting repeat drink driving offenders for assessment of alcohol-dependence. Promotion of the use of personal alcohol breathalyzer devices is also occurring. Support for interventions targeting first-time drink driving and drug driving offenders is lagging, however, despite a stated need for more effective partnerships to be built between the road safety and health sectors to better address issues involving alcohol and other drug use. Some technologies, notably dataloggers and vehicle tracking through GPS, offer promise of dealing better with impaired drivers, but there has been little policy development to date [9].

Canada

Previous research has shown that during the 1980s in Canada there was a reasonably consistent and rather dramatic decline in the percent of fatally injured drivers who were positive for alcohol [10]. The downward trend was clearly interrupted in 1991 when the percentage of fatally injured drinking drivers positive for alcohol increased to 48 %. But this increase occurred because the number of fatally injured non-drinking drivers declined but the number of fatally injured drinking drivers remained relatively stable. The percentage of fatally injured drinking drivers remained at 48 % in 1992. This reflects a decrease in both the numbers of non-drinking and drinking fatally injured drivers. From 1992 to 1999, there was an annual decline in the percentage of fatally injured drivers who tested positive for alcohol – i.e., a decrease from 48 % in 1992 to 33 % in 1999. The level achieved in 1999 was the lowest point reached in the past three decades and this downward trend strongly suggested a resurgence of the declines in the magnitude of the alcohol-fatal crash problem characteristic of the 1980s. In fact, both the decades of the 1980s and 1990s witnessed an initial increase in the magnitude of the problem followed by a consistent and comparable drop – reductions of about 30 % in both of these decades. It is, however, important to note that the decline in the percent of fatally injured drinking drivers that began in 1993 was again a function of two things – a decline in the actual number of drinking-driver fatalities, combined with an increase in the number of non-drinking driver fatalities. This divergence was particularly marked after 1996 and had a salutary effect on the percentage. Nonetheless, from 1992 to 1999, the absolute number of drinking drivers did decrease by 38 %, an amount slightly higher than the decrease in the percentage of fatally injured drivers who tested positive for alcohol – i.e., a 31 % reduction.

Since 1999, the percent of fatally injured drivers with positive BACs has increased to 38 % in 2001, declined to 35 % in 2002, increased to 38 % in 2003, and returned to 35 % in 2004 [11]. The number of motor vehicle deaths involving a drinking driver has also fluctuated in the range of 800 to 900 from 1999 to 2005. Figure 2 shows the number and percent of motor vehicle deaths involving a drinking driver in Canada from 1995 to 2005 [12].

This recent stagnation is corroborated by a 2007 public opinion survey conducted by the Traffic Injury Research Foundation (TIRF). TIRF found that progress in reducing the problem of drinking and driving appears to have halted. An estimated 1.84 million Canadians reported driving at least some time during the

Figure 2 Canada – number and percent of motor vehicle deaths involving a drinking driver. Source: TIRF.

past year when they thought they were over the legal limit, representing an increase from the 1.7 million reported last year. Of greater concern, the percentage of drivers who reported driving in the last 12 months when they thought they were over the legal limit has also increased steadily from 5.6% in 2004 to 8.2% in 2007. Finally, this year's survey also looked into public support for actions to control drinking and driving. Four measures garnered high levels of support among the public. These measures include: 1) mandatory use of ignition interlock devices for persons convicted of an impaired driving offence (83% of respondents agreed or strongly agreed with this measure); 2) tests of physical co-ordination in case the driver is suspected of being impaired by drugs or alcohol (80% agreed or strongly agreed); 3) immediate impoundment of the vehicles of drivers who fail a breath test (81% agreed or strongly agreed); and, 4) more police spot checks (70% agreed or strongly agreed). Transport Canada is actively working with the provinces and other partners to implement solutions as part of *Road Safety Vision 2010*, a program that seeks to make Canada's roads the safest in the world [13].

France

From 1983 to 2002 the number of injury accidents was reduced by more than half and from 1990 by almost one third (216 139 in 1983, 162 573 in 1990 and 105 470 in 2002). The number of fatally injured victims in crashes has also been reduced (from 11 946 in 1983, to 10 289 in 1990, and 7242 in 2002). There has also been a reduction in seriously injured victims (from 79 447 in 1983, to 52 578 in 1990 and 24 091 in 2002). The lowering of the BAC legal limit to 0.5% from 1996 would have been expected to increase the proportion of drivers over the legal limit, but this

does not appear to be the case. The data show that the prevalence of illegal alcohol levels as well as the proportion of alcohol related accidents did not increase and even tended to diminish since the end of the 90s, especially for fatal accidents. This progress is attributable to the massive alcohol screening enforcement. The number of random breath tests has risen steadily from the late 1980s to reach a high of 9.7 million in 2000 [14].

In the last few years, policies and public attitudes about driving have changed radically in France. The new policy includes dramatically stronger enforcement of speed limits with the installation of 1000 speed cameras, tougher penalties, and heavy media campaigns designed to stigmatize road violations as "road violence" and "road delinquency." This new policy, which started in July 2002 has had remarkable effects, decreasing traffic fatalities by 39% from 7720 in 2001 to 4709 in 2006. It has also decreased injuries (from approximately 150 000 per year to approximately 100 000 per year today). While the target of this new policy was speed, not impaired driving, vigorous enforcement also had an impact on impaired driving crashes. During this period, the proportion of alcohol related fatalities (where known) declined from 30.7% to 28.1% while the prevalence of positive BAC among all drivers has not changed (2.42% in 2004 to 2.46% in 2005). One logical conclusion from these trends is that, as drivers drive more slowly, crashes are less severe. With a similar level of alcohol impairment among drivers, fewer fatalities occur. In fact, the proportion of alcohol related accidents varied very little through the years, but as the total number of accidents has decreased significantly, alcohol followed the general pattern and alcohol related accidents are much less numerous nowadays than ten or even three years ago. Figure 3 shows the total number of

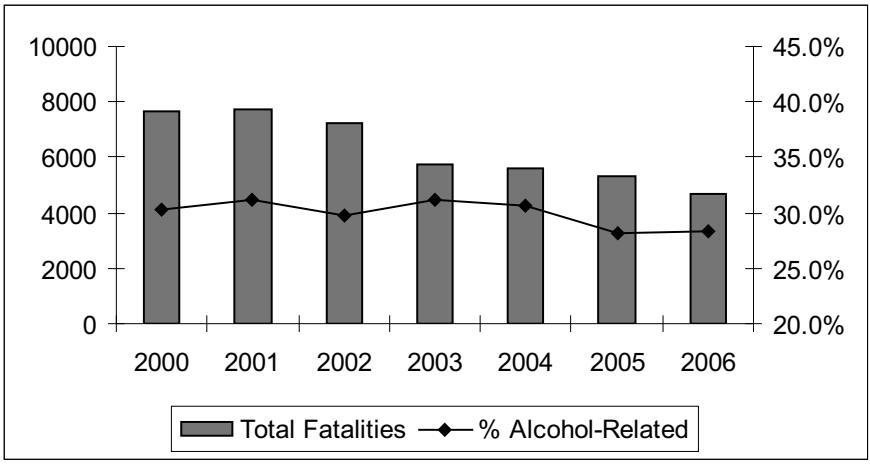

Figure 3 France – total fatalities and percent alcohol related (where known). Source: INRETS.

fatalities in road crashes in France and the percentage of alcohol related fatalities, where BAC test results were known.

One interpretation of the observed trend is that the presence of alcohol in traffic fatalities may not be influenced only by measures and policies concerning alcohol, but also by all the other types of traffic safety measures. In France, significant increases in speed enforcement also had a positive impact on alcohol related accidents; drivers drive more slowly (there was a major decrease of average speed during this period), accidents are less severe, and the same presence of alcohol results in fewer fatalities. This phenomenon needs confirmation by future data, and it would be interesting to see if similar results are can be obtained in other industrialized countries [15].

Germany

In the years after unification until 1993 trends in road accidents in general and especially alcohol related accidents worsened in the former East Germany. Figures from 1994 to 2002 show a general stabilisation and improvement in the development of road accidents throughout the country, especially with respect to related injuries and fatalities. But in 2002, the decrease of alcohol related accidents and casualties was lower than expected after the lowering of the BAC-limit to 0.5 %.

In 2005, 22 004 alcohol related injury accidents and 603 fatalities were registered in the official German accident database. These figures represent 6.5 % of all injury accidents and 11.2 % of all road accident fatalities. From 1995 to 2005 fatalities in road crashes declined from 9454 to 5361 – a drop of 43 %. In that same time period,

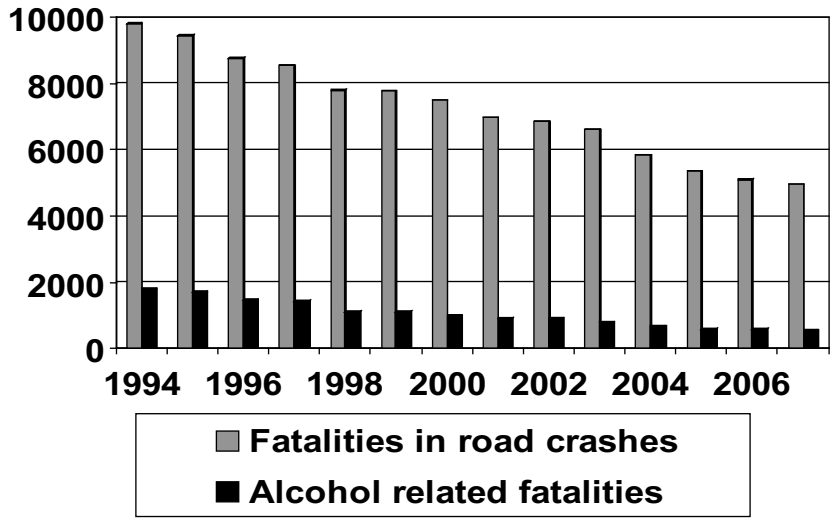

Figure 4 Time series of fatalities in road crashes and alcohol related fatalities in Germany. Source: BAST.

alcohol related fatalities declined from 1716 to 603 – drop of 65%. The share of alcohol related fatalities declined from 18.2% to 11.2% – a drop of 38%. The proportion of accident-involved road users influenced by alcohol decreased from 4.9 to 3.4% between 1995 and 2005, whereas the share of alcohol related casualties was reduced from 9.8 to 6.5% during the same period of time. Looking further back to 1975, the overall development of the number of casualties from 1975 to 2005 follows an even stronger downward trend. Fatalities in general have been reduced by more than two thirds from 17 011 fatalities in 1975 to 5361 fatalities in 2005 – reducing the number of fatalities in alcohol related accidents by more than 80% from 3461 fatalities in 1975. Progress continued in 2006; there were 5091 fatalities in road crashes, 599 of these were alcohol related. Figure 4 shows the trend for total fatalities and alcohol related fatalities from 1994 to 2006.

The overall trends in alcohol related injury accidents in Germany can be described as extremely positive, although the consequences of these accidents are still more severe than those of others. Efforts in enforcement and education can help to continue and accelerate this positive trend. Apart from other ongoing activities a long-term public campaign has been initiated by the German Road Safety Council in co-operation with Federal Highway Research Institute (BASt) to raise awareness of drink-driving – particularly among young drivers. Furthermore, legislation has recently been changed regarding the legal blood-alcohol limit for novice drivers and young adults. For these drivers, the legal BAC limit has been changed to 0.00% [6, 17].

The Netherlands

During the last 35 years the Dutch government was very successful in reducing drink driving. Increased enforcement levels, legal amendments and technological developments, along with national publicity campaigns and educational programs, resulted in a downward trend of drink driving as measured by roadside testing. The proportion of alcohol related fatalities decreased as well, although not to the same extent as the proportion of drink drivers on the road [18].

After a period with a more or less stable proportion of illegal BACs in roadside testing, the drink-driving trend decreased from 2003 to present. In 2003, special regional traffic enforcement units were established in all Dutch police regions, resulting in a higher enforcement level. At the same time new mass media campaigns were held and the proportion of offenders dropped from 4.1% in 2002 to 3.0% in 2006. However, the decline was solely visible among lower BAC levels ($\leq$.13%). Despite efforts of police and government, the proportion of high BAC offenders ($>$0.13%) did not decrease significantly over the past six years. Although the overall proportion of drink-driving offenders has dropped since 2000, the proportion of high-BAC drivers has remained the same [19]. In absolute terms the number of alcohol related traffic fatalities decreased between 2003 and 2006, since the total number of traffic fatalities in the Netherlands dropped by a quarter during the same period, from 1028 to 730 [20].

Young male drivers are at particularly high risk. While they represent only 4% of the population, they are involved in 13% of the serious injury crashes. In the case of drink driving, their involvement is even higher. Males from 18–24 form nearly a quarter of all alcohol-intoxicated drivers who are involved in serious injury accidents. In one case-control study, young male drivers were especially overrepresented in the groups testing positive for drug-alcohol and drug-drug combinations [21].

Regarding the high-BAC drivers, extra selective enforcement on high risk hours and places might be a successful measure. Increased random breath testing and more severe penalties do not seem to have had a significant effect. More can be expected from the implementation of an alcohol interlock program. The implementation of an alcolock program in the Netherlands is foreseen for 2009. This alcolock program will target high-BAC drivers and repeat offenders. The effect in terms of road safety will depend on the shape of the program, but expectations are high, based on the results of international evaluation studies [19].

Sweden

For a number of years, Sweden enjoyed a position as an example of successful work against drunk driving and its consequences. In the years around 1990 the proportion of alcohol related fatalities declined sharply – coming down from 31% in 1989 to 18% in 1997. This decline has a number of plausible causes. Firstly, on July 1, 1990, the legal BAC limit was lowered to 0.02% from the previous level of 0.05%. This step was evaluated by the Swedish Crime Prevention Council and they concluded that the lowering of the limit was associated with a 7% reduction of accidents overall, with an 11% reduction of single-vehicle accidents and with a 10% reduction of fatal accidents [22]. However, the lowering of the limit coincided with a very deep recession in the Swedish economy, which reduced by some 40% the proportion of young people who obtained their drivers licenses during the first year after having reached the age of licensing. This was also very favorable for road safety and this contribution may account for some 30% of the total effect of the lowering of the limit. Second, drinking-and-driving enforcement increased drastically and reached a peak in 1994, going from approximately 600 000 random breath tests per year to 1.8 million. Third, the penalties for drinking driving were upgraded. Finally, resources for attitudinal work directed towards ages 15 to 24 were tripled [4, 23].

Sweden joined the European Union in 1996. This meant, among other things, that it had to accept a gradual loss of its restrictive alcohol policies. The alcohol monopoly was partly broken; the ban on alcohol advertising now only applies to hard liquor; the import restrictions have been reduced. In conjunction with a recent reduction in alcohol taxes in Germany and Denmark, the pressure is now tremendously high on the Swedish Government to lower alcohol taxation. All of the deregulation moves which have been forced upon Sweden have led to a tremendous increase of alcohol consumption in the Swedish society. In 1996, the total alcohol

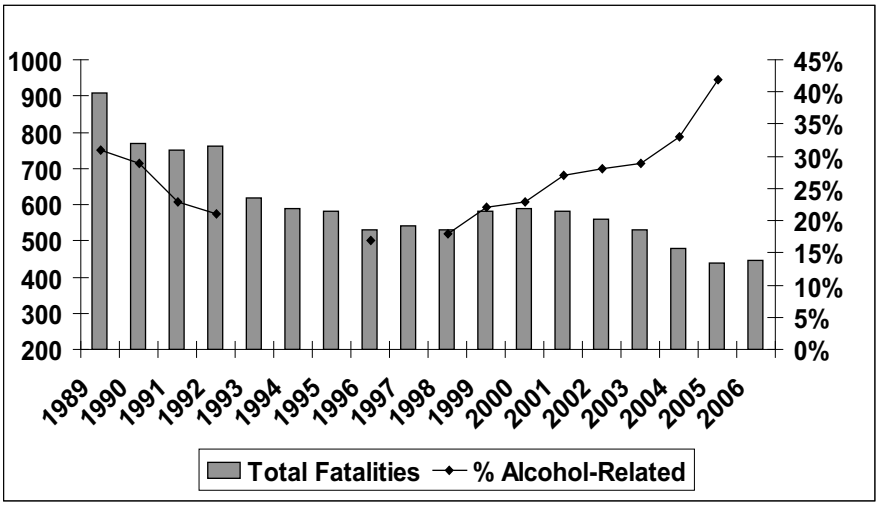

Figure 5 Sweden – total fatalities and proportion of fatally injured alcohol positive car drivers.

consumption level for persons older than 15 years of age was eight liters of pure alcohol per year. In 2004, this figure had risen to 10.5 liters. Instead of the 25% decrease, which was the World Health Organization goal, Sweden was faced with an increase of more than 25%. The relationship between total alcohol consumption and drinking and driving was studied in 1997 and it was found that if consumption increases by one liter, drinking and driving increases by 11% and fatal accidents by 8% [24]. There were also many more conflicts between transportation needs and consumption of alcohol [23].

In parallel with this development, Sweden has seen a 30% reduction of police enforcement of the 0.02% limit; in 1998, 68% of drivers charged with gross DUI were sentenced to imprisonment – in 2002 the proportion was down to 42%; in the same period, the resources for attitudinal "don't-drink-and-drive" campaigns were more than halved. Unfortunately, records also demonstrate that these factors have contributed to a corresponding increase in the involvement of alcohol among fatally injured drivers. The percentage of fatally injured drivers who had been drinking had risen from 18% in 1997 to 42% by 2006 [23]. Figure 5 shows the total fatalities in Sweden and the proportion of fatally injured alcohol positive car drivers.

The absolute number of alcohol positive fatalities remains almost exactly the same since 2000, The proportion has increased because of a decrease in the total number of fatalities. The total number of road fatalities in Sweden declined from near 600 in 2000 to fewer than 450 in 2006 (preliminary data indicates an increase to 470 total fatalities in 2007 [25]), while the number of alcohol related fatalities remained fairly constant at around 140 [20]. The gravity of this development is slowly being realized by the authorities, but many of the traditional tools to combat

the problem are no longer available. Most badly needed is a tangible increase in numbers of random breath tests. The government is now struggling to regain its position and actually had a target level for 2006 that was slightly higher than the previous peak level [23]. The importance of enforcement in general and of RBT in particular is illustrated by results indicating that an increase of the number of breath tests by 100 000 per year saves three to four lives [26].

Great Britain

The level of drink driving has been continually and consistently monitored in Great Britain since the late 1960s. A clear relationship is evident between the percentage of drivers killed in accidents who were over the UK limit (0.08 %) and the level of roadside breath tests conducted. Not until the introduction of evidential breath testing in police stations in 1983 did the situation radically change. This allowed a substantial increase in the number of roadside tests that could be carried out with the same traffic police resources. These increased from 200 000 per year in 1982 to 800 000 in 1998, with a consequent reduction in the level of drink driving. The percentage of driver fatalities over the drink drive limit dropped from around 30 % to 20 % over the same period. Although not independent of other activities such as the Department for Transport anti-drink-drive campaigns, this shows clearly the value of increased police roadside enforcement in reducing drink driving. Indeed, in the late 1990s and onwards, despite sustained high levels of anti-drink-drive campaigning there is evidence that reductions in the levels of roadside breath testing are again leading to increased levels of drink driving [4]. The number of people

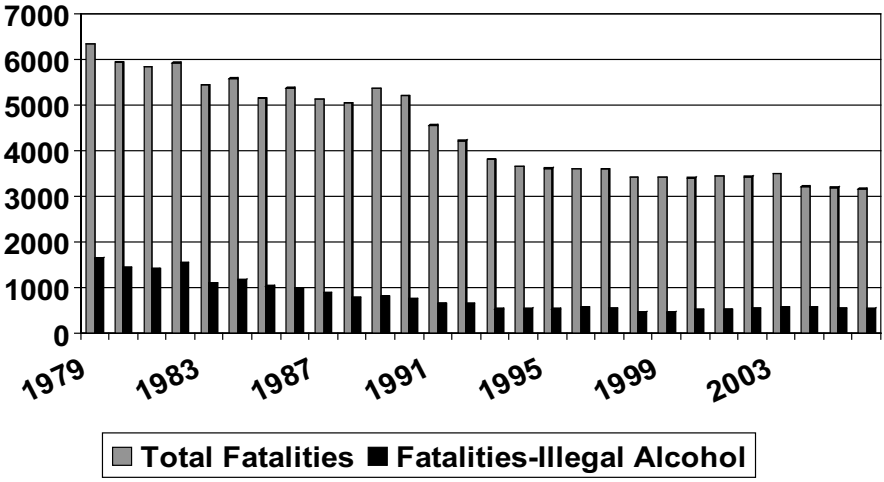

Figure 6 Great Britain – estimates of fatalities involving illegal BACs (> 0.08 %) and total fatalities. Source: Road Casualties Great Britain 2006.

killed in drink-drive accidents fell to a low of 460 deaths in 1998, but has since risen, to an estimated 540 deaths in 2006. The number of roadside screening breath tests reached a peak of 816 000 in 1998, and fell steadily to 534 000 in 2003, but increased to 578 000 in 2004. The total number of road fatalities declined steadily from around 5200 in 1990 to 3650 in 1994. For the next ten years there was no clear pattern, as fatalities varied between 3400 and 3600. Fatalities did decline further to 3221 in 2004 and to 3172 in 2006. [27]. Figure 6 shows the total number of fatalities and the estimates of fatalities involving illegal BACs (0.08%).

A number of measures are being considered to combat this rise, including an extension of drink-drive rehabilitation courses, evaluation of the value of breath alcohol interlocks and the practicality of evidential roadside breath testing. Although the number of pedestrians killed with a BAC exceeding the drink-drive limit 1979–1999 has fallen by about 50%, from nearly 600 to around 300, the proportion with a BAC exceeding the drink-drive limit has risen from 33% to 39% [28].

Legislation was enacted in 2005 to allow for roadside evidential breath testing, but thus far no devices have received government approval for police use. It is expected that such approval will be authorized during 2008. In a parallel initiative the development of roadside breath screening devices which record both personal and demographic data is also being encouraged for UK use. Both actions are aimed at tackling an increasing trend in drink driving over recent years [29].

United States

After 15 years of decline, in the last decade the percentage of fatal crashes that involve alcohol has stalled at about 40%. From 1982 to 1999, rates of alcohol related (BAC > .00) crashes declined, as did the total number of alcohol related crashes in the United States. In 1982, there were 26 173 alcohol related fatalities in the United States, 60 percent of the total number of people killed on U.S. roadways. By 1999, that percentage had fallen to 40 percent and alcohol related fatalities fell to 16 572; decreases of 33.3% and 36.7% respectively. The most dramatic declines occurred from 1982 to 1994 [30].

Unfortunately, in 2006 there were increases in the number and rate of alcohol related fatalities. In fact, the number of people killed in alcohol related crashes was the highest since 1992. In 2006, alcohol related fatalities rose slightly (17 590 in 2005 to 17 602 in 2006). Since the number of total deaths in crashes dropped in 2006 (42 642 compared to 43 510 in 2005) there was an increase in the percentage of alcohol related traffic fatalities to 41 percent (up from 40 percent in 2005 and 39 percent in 2003 and 2004) [31]. Figure 7 shows the total and alcohol related fatalities in the U.S. from1982–2006.

Some have argued that the decrease in alcohol related crashes in the last 25 years resulted from a reduction in impaired driving by the easy-to-deter drinking drivers, whereas the “hard core” drinking drivers remain to be controlled. Evidence, however, does not indicate a change in the characteristics of crash-involved drinking drivers during the last 20 years. Reductions in fatalities have occurred equally at all

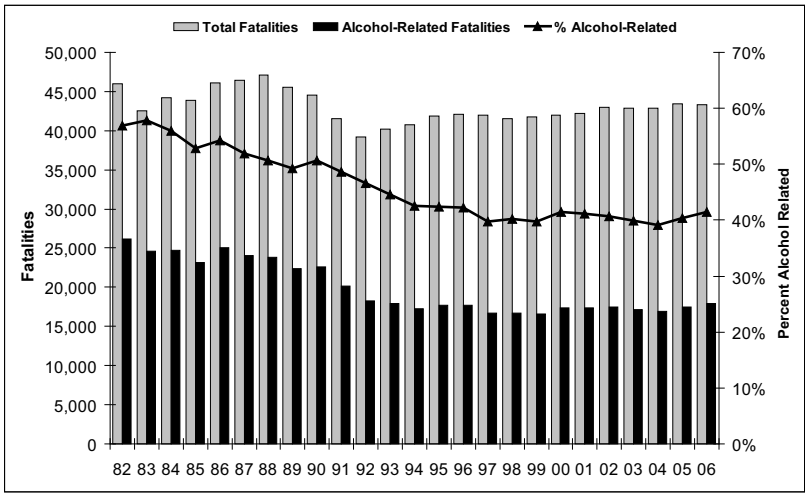

Figure 7 U.S. total and alcohol related fatalities 1982–2006. Source: NHTSA.

BAC levels. It is apparent that policies, enforcement levels, geographic and other factors play a role in determining the level of alcohol involvement in traffic crashes in the U.S. States vary widely in the involvement of alcohol in fatal crashes with state-to-state percentages of fatal crashes involving alcohol ranging from 13 % to 55 % in 2005 [32].

The lack of progress may in part result from the fact that, while many effective strategies are well known, they are not implemented as widely or as vigorously as possible. For example, as discussed above, many countries have experienced a significant decrease in alcohol impaired crashes along with the implementation of strong random breath testing enforcement programs. In the U.S., while random breath testing is not legally permissible, sobriety checkpoints (which have been shown to have similar impacts) are widely permitted – but not widely used [33]. Thus, stronger implementation of effective strategies could result in further progress.

Despite the potential for better implementation of existing strategies, the argument can be made that we are approaching the limits of policy and deterrence to suppress impaired driving. This possibility, along with the dramatic advances in technology, has led some advocates and policy makers to promote the wider application of technological approaches to preventing impaired driving [30]. These approaches could include wider implementation of alcohol interlocks for impaired driving offenders. Interlocks have been shown to be effective in reducing recidivism when used. More states in the U.S. are passing laws mandating interlocks for more offenders, including first offenders in some instances. The technology for interlocks is well developed. New technologies are being explored that could be applied to all vehicles to prevent operation by drivers who are over the legal limit

for alcohol or who are otherwise impaired. These technologies may be farther in the future, but have the potential for a dramatic impact on impaired driving.

Worldwide trends in drug impaired driving

While trends in drinking and driving have been tracked by most industrialized countries for many years, the same can not be said for drugged driving. Quite a lot of information has emerged in recent years about the presence of drugs other than alcohol in fatally injured drivers in a number of countries. Since the collection of such data is relatively recent, tracking of trends is rather limited. However, trend data is available in a few countries, not only from testing of fatally injured drivers, but also from roadside surveys and from other sources.

Norway has been in the forefront of testing drivers for drugs. One study compared alcohol and other drugs found among single fatal accident drivers in Norway in 1989–1990 with similar fatally injured drivers in 2001–2002. Those drivers positive for drugs increased from 12.4% in 1989–1990 to 22.8% in 2001–2002. For those drivers positive for alcohol and drugs, the percentage increased from 8.9% to 17.4% in the same time period. Those drivers positive for alcohol alone dropped from 32.9% to 23.9%. Figure 8 compares the drug positive results for the two time periods [34].

In the *United States*, a study [35] examined the change in alcohol and drug use in fatally injured drivers in Washington State from 1992/1993 to 2001/2002. The data revealed that over the decade, while alcohol use by fatally injured drivers had declined (47% to 44%), some drug use, notably methamphetamine, had increased significantly from 1.89% to 4.86% between 1992 and 2002. While alcohol positives have decreased in 2002, the average BAC remained unchanged at 0.17%. Drugs and alcohol were present in 62% of cases in 2002, which was unchanged from 1992. Of those alcohol positive in 2002, there was a significant increase in drug positives – from 10% to 17%. There was a significant increase in drug positives overall – from 25% to 35%. It was indicated that the increased methamphetamine detection reflects increased use, while the increases in other drug positive rates came primarily from analytical improvements. Table 1 compares the drug and alcohol test results for the two periods. Table 2 compares the results by drug category for the same periods.

Recent evidence has suggested that illicit drug taking in *Great Britain* has increased considerably since the mid 1980s. Results from a 2000 study showed that at least one medicinal or illicit drug was detected in 24.1% of the 1184 casualties tested [36]. Since the previous survey in the late 1980's the incidence of illicit drugs detected has increased from 3% to around 18% whereas the incidence of medicinal drugs remained at around 6%. There was a substantial increase in the incidence of cannabis in fatal road casualties from 2.6% to 11.9% between 1989 and 2001. Table 3 compares the results for the two periods.

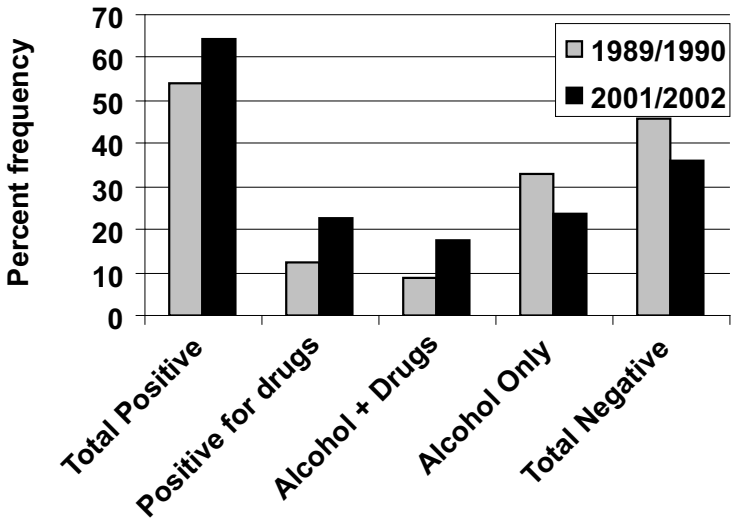

Figure 8 Comparison of alcohol and other drugs among single fatal accident drivers in Norway 1989–1990 (n = 79) and 2001–2002 (n = 92). Source: ICADTS Oslo 2005 Symposium – Christophersen.

Drug use among drivers in the *Netherlands* has apparently increased over the last twenty years. In the mid 1980s a study in Rotterdam hospitals showed that 5% of the injured drivers had used drugs. In a recent study in the town of Tilburg nearly 20% were found to be positive [37]. The Dutch government is aware of the increasing problem of drug use in traffic and the minister of Transport has announced stricter legislation and enforcement.

The first report on trends over time in cannabis use and driving in *Canada* appeared a few years ago. Researchers compared the proportions of Ontario adults reporting driving under the influence of cannabis (DUIC) in a representative sample

Table 1 U.S. – Washington State fatally injured drivers alcohol/CNS drug detection comparing 1992–1993 with 2000–2001 (Source: ICADTS T2004, Logan).

	Alcohol Negative	**Alcohol Negative**	**Alcohol Positive**	**Alcohol Positive**		
	1992/1993	2000/2001	1992/1993	2000/2001	1992/1993	2000/2001
Drug Negative	38%	38%	37%	27%	75%	65%
Drug Positive	15%	18%	10%	17%	25%	35%
Year Totals	53%	56%	47%	44%		

of the Ontario population surveyed in 2002 with those reported earlier. A trend for an increase over time was observed, with the proportion of adult drivers reporting DUIC increasing from 1.9% in 1996/97 to 2.7% in 2002. It was noted, however, that this increase was not statistically significant [38].

Table 2 U.S. – Washington State fatally injured drivers positive for drugs (Source: ICADTS T2004, Logan).

	1992/93	2001/02
Marijuana	11.01%	12.7%
Cocaine/met	3.14%	3.51%
Amphetamines	1.89%	4.86%
Benzodiazepine	1.26%	4.05%
Diphenhydramine	0.63%	2.70%

Table 3 U.K. – Drugs in Road Fatalities (Source: Tunbridge in Sweedler et al., *Traffic Injury Prevention* (Vol. 5, No. 3)).

	1989	2001
% Illicit	3%	18%
% Licit	5.5%	6%
Cannabis	2.6%	11.9%
Some Alcohol	35%	31.5%
Alcohol > .08	25%	21.5%

Conclusions

As is apparent from the discussions above, the worldwide trends in impaired driving have some common threads and many variations. Most countries experienced declines in total road fatalities and alcohol related crashes and fatalities from the early 1980s to the early 1990s. In the first half of the new century, progress in many countries has stalled. Through 2006, in the U.K, U.S., Canada and Australia the number of fatalities in road crashes has not changed very much. The number of alcohol related fatalities has also been fairly constant in that time period. In Sweden the total number of fatalities dropped from the 1970s through the 1990s, went up in 1999 and 2000, but again continued to drop until 2007, when there was an increase. The number of alcohol related fatalities also dropped through the mid 1990s, but has remained fairly constant since. In France and Germany, both total and alcohol related fatalities have continued to fall through 2006.

Stronger laws, vigorous enforcement, and changes in social norms have all contributed to the progress that has been made. A number of countries found a strong link between levels of enforcement (especially random and roadside breath tests) and alcohol related fatalities. When the number of breath tests increased, alcohol related fatalities dropped. When the number of tests dropped, alcohol related fatalities increased. Complacency and a deflection of attention to other issues in recent years have been difficult to overcome in some countries. Harmonization of traffic safety laws in the European Union has strengthened laws in some countries but threatens existing strong policies in others. It may be that the major gains have already been made in many countries and that additional progress will require a much greater level of scientific knowledge, use of new technologies and political and social commitment to implement proven countermeasures.

While alcohol impaired driving has decreased, drug impaired driving appears to have increased. More testing, improved testing methods and accuracies, and case controlled studies are still needed, but data from a variety of sources have shown significant increases in drug use and driving. In addition, there has been a large increase of drivers using combinations of alcohol and drugs.

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Drugs, driving, and models to measure driving impairment

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Abstract

Research into the effects of various drugs on driving performance is becoming more important as epidemiological studies indicate that the incidence of drugs in drivers is increasing. Considering that this type of research is likely to guide laws and behaviours, it is important that the tests being used to determine whether certain drugs are impairing are sensitive, valid and reliable. This chapter presents the most common tests used in research to evaluate behaviours relating to driving. The research varies from the use of simple cognitive tasks, to simulators, and to driving in real traffic. The findings suggest that there are limitations to various methods of testing; however, considerations and precautions can be taken to ensure that we measure relevant processes and use sensitive tests for drug impairment.

Introduction

Driving is a complex task that requires control and coordination of a number of different behaviours. These behaviours are typically divided into three hierarchical levels of control [1]. At the top level or the strategic level, executive decisions such as route-choice and planning, setting of trip goals (e.g. avoid peak hour), observation, judgment and understanding of traffic and risk assessment are made. At the intermediate level or the manoeuvring level, negotiations of common driving situations occur. These behaviours are described as controlled and require conscious processing: reactions to the behaviour of other drivers, distance-keeping, speed adjustment, negotiation of curves and intersections, gap acceptance, and obstacle avoidance. At the lowest level or the operational level, the basic vehicle-control

processes occur, such as steering, braking and gear shifting, and are described as automotive behaviours. Automotive behaviours require little conscious mental activity and develop following extended practice. To gain a complete picture of the extent to which drugs affect driving performance, a variety of tests are used that measure behaviours across all three levels of control. The following chapter aims to identify the most common tests used to assess the impact of drugs on driving and how sensitive those tests are to drug effects.

There are three approaches used to assess driving impairment: on-road tests, driving simulators, and laboratory tasks. On-road driving tasks can be measured using two different methods. The first method, naturalistic driving scenarios, in which participants drive in actual traffic, are subjectively scored by trained raters. During these tests a licensed driving instructor, who has access to dual controls should an emergency situation arise, is accompanied by an observer who scores the participant according to a number of simple and strict criteria. The second method used to assess driver performance measures actual responses as driver inputs from steering, braking, and acceleration controls. These tests take place on both open and closed driving courses. It is often argued that on-road driving tasks are the gold standard tests to determine driver impairment. However, while these tasks effectively measure lower level behaviours, for obvious safety reasons they can not measure higher level functions such as response to emergency situations and risk taking behaviours.

Driving simulators offer the ability to assess higher level behaviours in a safe and controlled manner. However, they vary widely in research studies across different laboratories, thus making comparison difficult. They range from fully interactive systems, where the participant is seated in a complete vehicle mounted on a motion platform with 360-degree views, to desk top systems where the road environment is viewed on a computer screen and controlled by a steering wheel, keyboard or mouse. Driving simulators are often criticized for limited realism and it is questionable as to how well the results translate to real life driving situations. Additionally, the perceived risk of driving in the simulator is much less than on the open road, so participants may adjust their behaviour accordingly, e.g. driving less cautiously.

Cognitive tasks enjoy the benefit of permitting an assessment of a single, isolated aspect of driving performance in a controlled environment; however, there is a question as to whether they are comparable to real-life driving and whether they can be accurately used to predict accident risk.

Which tests are sensitive to drug effects on driver performance?

Automative behaviours

Road tracking task

The most common on-road test used to measure driver impairment is the road tracking task [2]. Participants are required to drive a 100 km course maintaining a constant speed of 95 km/h and a steady lateral position in traffic lanes: the standard deviation of lateral position or SDLP. SDLP is an index of road tracking error or weaving, swerving and overcorrecting. SDLP is measured using an electro-optical device mounted on the rear of the vehicle which continuously records lateral position relative to the traffic lane. An increase in SDLP, measured in centimeters, indicates driver impairment, as the driver's ability to hold the car in a steady lateral position diminishes.

A paper by Robbe [3] described three studies assessing the effect of marijuana on driving using the road tracking task. The first study utilised a shortened version of the road tracking task to assess the effects of marijuana containing three different THC (Δ-9-tetrahydrocannabinol) doses (100, 200 and 300 μg/kg) on driving. The test was undertaken on a restricted highway in which participants were required to maintain a constant speed of 90 km/h and a steady lateral position over a 22 km road-tracking course. SDLP, mean lateral position, and the mean and standard deviation of speed were recorded. The tests were undertaken at 40 minutes and one hour after smoking marijuana. The results revealed that all three THC doses significantly affected SDLP relative to placebo and that impairment after marijuana was equivalent at both time points. These results were compared to those of alcohol and suggest that THC consumption produces similar effects to BACs (blood alcohol concentration) of 0.03 % to 0.07 %. Other variables were not significantly effected by marijuana. The road tracking task in the second study involved driving on a 64 km highway course in the presence of other traffic, with the aim of maintaining a steady lateral position. The findings confirmed that driving performance was impaired in a dose related manner by THC, with SDLP increasing to 3 cm in the 300 μg/kg dose condition. The third study assessed the combined effects of alcohol and marijuana on driving ability and was conducted on an open highway in the presence of other traffic. Participants were administered alcohol (BAC 0.04 %) combined with a dose of THC (100 or 200 μg/kg), and either alcohol or marijuana alone. SDLP was measured over a 40 km section of highway and was found to increase compared to placebo in all drug conditions. The combination of alcohol and the low dose of THC resulted in an increase in SDLP equivalent to a BAC of 0.09 %, and the combination of alcohol and the higher dose of THC produced an effect equivalent to a BAC of 0.14 %.

The road tracking task has also been used to assess the effect of MDMA (3,4 methylenedioxymethamphetamine) (75 mg, 100 mg) and alcohol (BAC to reach

0.06), both combined and alone, on driving performance [4]. The results demonstrate that SDLP was significantly affected by all treatment groups. Alcohol increased SDLP by 2.5 cm and both MDMA doses decreased SDLP by approximately 2 cm relative to placebo. Both doses of MDMA significantly decreased the SD of speed by about 0.2 km/h compared to placebo. No other measures were significant. These findings were partially supported by Ramaekers et al. [5] who reported that participants administered 75 mg of MDMA showed a decrease in SDLP relative to placebo; however, no significant results were found for SD of speed. Once again lateral position and speed were not affected by MDMA.

Critical tracking task (CTT)

The critical tracking task is a psychomotor test that measures eye-hand coordination and delays in visual motor response. The CTT is a simple test that measures a subject's ability to control a displayed error signal. An error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Compensatory joystick movements null the error by returning the cursor to the midpoint. The frequency at which the subject loses control is the critical frequency or Lambada-c. It has been suggested that the CTT is the closest laboratory alternative to the Road Tracking Task [5].

Research into the effects of marijuana have demonstrated that the CCT is sensitive to the impairing effects of marijuana. This is supported by recent literature that supports some impairment relative to placebo on CTT after the consumption of THC up to six hours after drug taking [5]. The CTT has also been used to assess impairment due to MDMA (75 mg, 100 mg) and alcohol (BAC to reach 0.06), combined and alone [4]. The authors reported that alcohol impaired tracking performance as shown by a decrease in Lambada-c in the alcohol conditions compared to the placebo condition. However, no significant effects were shown for MDMA or MDMA by alcohol.

Control behaviours

Object movement estimation under divided attention (OMEDA)

Assesses the participants ability to estimate speed of movement, and time to contact (TTC) of a moving object to a fixed point under divided attention. Participants are presented with a computer screen, the corners of which are covered by green triangles and the centre of the screen is occluded by a yellow circle. The participant views a target (a red dot) travelling from the corner of the screen to the edge of the yellow circle and the target then passes out of view behind the circle. The participant's primary task is to indicate, by using a foot pedal, when the target reaches the centre of the computer screen. While the target is moving, participants complete a secondary task; they are required to indicate whether a geometric shape that ap-

pears on the yellow occlusion circle is the same as any of the shapes which appear on the four green corners of the computer screen. The main variable is the absolute mean difference between the estimated and actual TTC.

Kuypers et al. [4] assessed the effect of MDMA (75 mg, 100 mg) and alcohol (BAC to reach 0.06), combined and alone on driving skills using the OMEDA. The authors report no significant effects for any of the conditions compared to placebo. However, using a more complex version of the OMEDA Lamers [6] found that a single dose of MDMA 75 mg decreased the subject's ability to estimate TTC, indicating that the complex version of OMEDA is more sensitive to drug effects. Additionally, the results suggest that assessing performance as close to T_{max} as possible renders best results.

Visual search task

Lamers and Ramaekers [7] assessed participants' eye movements in a City Driving Test using a head-mounted eye tracking system. The device records a subject's line of gaze with respect to the head, which is used to determine visual search for vehicles proceeding with right of way on the right of 58 intersections along the route. Checking for traffic at intersections was the dependent variable. The results revealed that only the combination of THC and alcohol significantly reduced visual search frequency compared to placebo (by 3 %).

Car following task

The car following task was developed to measure attention and perception performance, as errors in these areas often lead to accident causation [8]. In this task participants are required to match the speed of a lead vehicle and to maintain a constant distance from the vehicle as it executes a series of deceleration and acceleration manoeuvres. The primary dependant variable is reaction time to lead vehicle's movements and distance maintained during manoeuvres or headway. This test assesses a driver's ability to adapt to manoeuvres of other motorists.

Robbe [3] investigated the effects of marijuana (100, 200 and 300 µg/kg) on driving performance using the car following test on a 16 km segment of highway traffic (15 min test). The lead vehicle's speed varied between 80 and 100 km/h with one deceleration and acceleration manoeuvre taking approximately 50 seconds to complete. Depending on traffic density, six to eight of these manoeuvres were executed during one test. The results revealed that reaction time increased for each THC dose compared to placebo; however, the findings did not reach significance. In relation to the distance maintained, participants in the THC condition lengthened their headway (mean distance from the lead vehicle), indicating that participants were more cautious in the marijuana conditions. In a second study, using an improved car following test (microprocessor-driven cruise-control), a significant change increase) in the mean reaction time to speed adjustments of the lead vehicle

was found for the combination of alcohol and 200 THC μg/kg (4.65 s placebo to 6.33 s alcohol and THC). Headway distance was also significantly impaired by alcohol and THC conditions (5.69 min placebo to 7.78 min drugs).

Kuypers et al. [4] assessed the effect of MDMA (75 mg, 100 mg) and alcohol (BAC to reach 0.06), combined and alone on driving performance using the car following test. In addition to the method described above, the investigator in the lead car also randomly activated the brake lights. When this occurred, subjects were instructed to remove their foot from the brake pedal as quickly as possible. The results revealed that performance was unaffected by MDMA alone and that alcohol increased brake reaction time. When alcohol was administered alone or in combination with 75 mg MDMA, reaction time increased by 20 ms compared to placebo. When alcohol was combined with 100 mg MDMA reaction time further increased by 60 ms, indicating that MDMA may worsen the effects of alcohol. No significant effects were found for other measures.

Sobriety testing

Sobriety tests measure psychomotor performance, cognitive functioning, and divided attention. In addition to maintaining coordination and balance, the individual is required to remember instructions and simultaneously perform more than one task at a time. The most common battery of performance tests are known as the Standardised Field Sobriety Tests (SFSTs) and comprise the horizontal gaze nystagmus, one-leg stand, and walk and turn tests.

The SFSTs have been demonstrated to be a valid measure to identify alcohol intoxication [9–12]. A laboratory study by Tharp et al. [9] investigated the efficiency of the SFSTs in identifying alcohol intoxication and demonstrated that the SFSTs accurately classified 81 % of subjects as either above or below 0.10 % BAC. A later study by Burns and Anderson [11] examined field data collected from experienced police officers using the SFSTs. The results revealed that the police officers correctly classified 86 % of drivers with a BAC reading of above or below 0.1 %. Drivers over the limit were correctly identified in 93 % of cases, and drivers below the limit were correctly identified in 64 % of cases. The SFSTs have also been shown to be efficient (94 %) in detecting BAC levels between 0.04 and 0.08 % [11].

Papafotiou et al. [13] assessed whether the SFSTs (as used by Victoria Police, Australia) provide a sensitive measure of impairment following the consumption of a cannabis. Participants consumed cigarettes that contained either 0 % THC (placebo), 1.74 % THC (low dose) or 2.93 % THC (high dose). After smoking a cannabis cigarette, participants performed the SFSTs and a simulated driving test within two hours after the smoking cannabis. The results revealed that there was a positive relationship between the dose of THC administered and the number of participants classified as impaired based on the SFSTs. The percentage of participants whose driving performance was correctly classified as either impaired or not impaired based on the SFSTs ranged between 65.8 % and 76.3 %, across the two THC conditions. The results suggest that performance on the SFSTs provides a moderate predictor of driving impairment following the consumption of THC [14].

Executive planning

The Tower of London (TOL)

A decision-making task that measures executive function and planning [15]. The task consists of computer generated images of begin- and end-arrangements of three coloured balls on three sticks. The subject's task is to determine as quickly as possible whether the end-arrangement can be accomplished by "moving" the balls in two to five steps from the beginning arrangement by pushing the corresponding number coded button [16]. The total number of correct decisions is the main performance measure. Ramaekers, et al. [5] found that THC significantly decreased the number of correct decisions on the Tower of London task. Results also indicated that a longer planning time was required at 45 min after the consumption of a high THC dose.

The city driving task

Measures aspects at both the control level (e.g. maneuvering, distance keeping, speed adjustment) and the strategic level (observation and understanding of traffic, risk assessment, and planning).

A study by Robbe [17] was conducted in urban traffic with the aim of assessing whether THC impairment is greater using a more complex and demanding driving test. The test involved driving a 17 km course within the city limits of Masstricht, through heavy, medium, and low density traffic, under the influence of 100 μg/kg THC and alcohol 0.05% BAC. Tests were conducted during daylight hours at the same time and day of the week. Two different scoring methods were used: a "molecular" approach and a "molar" approach. The first "molecular" approach required a specially trained observer to record when the participant made or failed to make a series of observable responses at predetermined points along the route according to strict criteria. This method indicated that neither alcohol nor marijuana significantly affected driving performance. The second "molar" method involved the driving instructor retrospectively rating the subjects' driving performance using a shortened version of the Royal Dutch Tourist Association's Driving Proficiency Test. In total, 108 items were scored as either pass or fail and were categorized in the following subgroups: vehicle checks, vehicle handling, traffic maneuvers, observation and understanding of traffic, and turning. The percentage of items scored as "pass" was calculated as the total test performance measure. This approach proved to be more sensitive, with alcohol (0.034% BAC) significantly impairing driving when compared to placebo. However, the low dose of marijuana did not impair driving performance on any of the variables.

A similar city driving test was used by Lamers et al. [7] to assess the effects of alcohol (0.04 to 0.05% BAC) and marijuana (100 μg/kg) on driving and was scored using a 90 item version of the Royal Dutch Tourist Association's Driving Proficiency Test. Participants drove a constant route through business and residential areas on mostly two lane undivided streets and a 5 km, four lane divided section on a major cross-city thoroughfare. The study did not support Robbe's [17] findings,

with none of the driving variables significantly affected by alcohol, THC or the combination of the two.

Limitations of these tests or approaches include the fact that the recorded impairment is subjective and retrospective. In general, the results suggest that these approaches to testing for impairment are not always sensitive to drug effects. In addition, in naturalistic studies it is often difficult to control the testing scenario, whereby one participant's test may vary to the next depending on traffic, weather conditions and other factors. The potential effect of external factors should also be taken into consideration when assessing driving in real traffic.

Driving simulators

Assess behaviors across all three levels of control. Discussed below are a few recent studies which utilize driving simulators to assess driver performance.

A series of studies conducted at the Swinburne University assessed simulated driving performance after the administration of marijuana, marijuana and alcohol, dexamphetamine and methamphetamine using the CyberCAR LITE simulator. Participants were seated at a bench attached with a "force feedback" steering wheel with accelerator and brake pedals placed underneath the bench. The driving environment was projected on a 175 × 120 cm white screen, which placed the participant inside the vehicle with a view through the front windscreen and included a simulated car dashboard (speedometer, gears, rear-view mirror, and side-view mirrors). Participants completed four scenarios: freeway driving and city driving during both day time and night time conditions, with each taking approximately five minutes to complete. Thirty-four or fewer variables were continuously recorded to measure a range of driving behaviours and errors. They included collisions, signal errors, speed control, safe following distance, weaving, and response to an emergency situation (tree falling across road on freeway or car running a red light). Each variable score was then multiplied by a loading factor which represented the severity of the error. All adjusted scores were then summed to give an overall rating of "impaired" (76+) or "not impaired" (0–75). Marijuana significantly impaired performance on measures of lane weaving [14]. An overall reduction in driving performance was reported for the dexamphetamine condition compared to placebo in the day time scenario (in particular signalling errors and stop sign/lights adherence). This impairment was not observed for the night time condition [18].

To overcome some of the limitations of laboratory testing, such as low to moderate drug doses and unrealistic testing times and environment, Krueger & Vollrath [19] tested participants in a social setting in front of Discotheques. They selected participants who were under the influence of drugs and who indicated that they had been driving or would drive in similar circumstances (under the influence of recreational doses of drugs). Testing was undertaken on weekends between 10 p.m. and 6 a.m. at 29 discotheques across Bavaria, Germany. Participants were tested using a driving simulator that consisted of a 15-inch computer monitor and a commercial joystick steering wheel. The primary task involved the participant holding the vehicle in a steady lateral position while driving a curved road with a speed limit of

80 km/h. Four secondary tasks were also presented at random intervals. A simple reaction time task required participants to brake as fast as possible when they heard an acoustic signal resembling an ambulance horn. A peripheral attention task required participants to watch two traffic lights, one at each top corner of the screen. At random points in the simulation the traffic lights changed colour then turned red, at which point a bar appeared directly in front of the car. Only by reducing speed when the lights began to change could an accident be avoided. The third task assessed controlled reduction of speed; when a stop sign was presented, participants were instructed to come to a complete stop in front of the sign. The final task assessed risk-taking behaviour; a busy crossroad was presented and participants were to cross only when they thought the gap was large enough for them to do so safely.

Krueger & Vollrath [19] reported, using a factor analysis, that three factors representing driving performance: SDLP; speed; and performance in the secondary tasks. Blood sample results distinguished the following groups: THC (indicating recent cannabis use), THC-COOH (indicating past cannabis use), low concentration amphetamines (less than 0.05 mg/l), and high concentration amphetamines (greater than 0.05 mg/l). Results were analysed for each drug group alone and in combination with alcohol. In contrast to on-road studies, the results revealed that THC improved SDLP. Neither speed nor performance in the secondary tasks was affected. The THC-COOH group showed a further improvement in SDLP, as well as a reduction in speed. However, when combined with alcohol, performance was seen to deteriorate, especially in the THC-COOH group. For high concentration amphetamines, average speed increased slightly and performance in the secondary tasks deteriorated. In line with road tracking studies, low concentration amphetamine was associated with decreased SDLP. However, when combined with alcohol, SDLP increased dramatically. When cannabis was combined with high doses of amphetamines, SDLP increased and performance in the secondary tasks was impaired. When alcohol was combined with cannabis and amphetamines, performance was worse on all three measures. While the consumption of a single drug may variably affect driving performance, it is apparent that consuming a combination of drugs will have a dramatic and deleterious effect on driving performance.

A similar quasi-experimental methodology was used by Brookhuis et al. [20] who assessed volunteers after self administration of an MDMA tablet and after poly drug use. Participants completed a first ride in a driving simulator at the research institute one hour after the consumption of MDMA (average 59 mg). Participants then attended a party and were instructed that they could consume any psychoactive substance they liked, just as they normally would. A second ride in the simulator was undertaken after the party: the poly drug condition. The majority of participants consumed additional MDMA (70 %) and all had consumed other drugs at the party, most commonly marijuana (80 %) and alcohol (90 %). Participants returned for a final ride in the simulator on a separate evening when not under the influence of drugs. Driving behaviour was assessed in a fixed-based driving simulator consisting of a car with the original controls attached to a Silicon Graphics computer, the road environment was projected on a semi-circular screen. Road tracking (SDLP and speed) was assessed to reflect performance of automotive behaviours. Car following performance (delay in response to speed changes, headway) and per-

formance when lead traffic came to a standstill (brake reaction time) were measured to reflect control behaviours. Executive behaviours were assessed using a few scenarios: gap acceptance was measured while crossing a major road with traffic travelling in both directions, again whilst turning left with approaching traffic, and risk taking was assessed by the participant's response to a traffic light turning yellow. The results revealed that road tracking was sensitive to drug effects with SDLP increasing significantly in the multi drug condition. Speed measures also increased significantly from the no drug condition to the MDMA condition to the poly drug condition. Participants in the poly drug condition were more likely to accept less clearance than in the no drug condition. Car following performance revealed a trend for smaller headway in the poly drug condition (not significant). Reaction time when the lead car came to a standstill did not differ between conditions; however, the standard deviation in reaction time increased from no drug to MDMA to the poly drug condition. In the no drug condition, accidents occurred in two of the 20 no drug drives (10%). Under the influence of MDMA participants crashed four times (20%) and when under the influence of multiple drugs participants crashed five times (25%) while driving. The main limitation of previous quasi-experimental methods is the lack of experimental control; however, they do benefit from greater realism and testing the effects of realistic ('street') drug doses.

Validity of tests measuring driving or skills related to driving

A wide range of experimental studies have assessed drug effects on laboratory test performance over the last three decades. Although various investigators have claimed that their task or task battery taps driving related skills, most studies show no proof for such a claim or even a reasonable theoretical rationale. In general, investigators have employed a wide range of laboratory tests measuring aspects of perception, attention, motor control, cognitive function or CNS arousal that are assumed to underlie safer driving. However, none of these tests has ever been shown to closely predict driving performance or traffic accidents. Experimental laboratory tests may predict driving impairment, but until now it simply has not been demonstrated.

Two causes can be identified that have hampered attempts to demonstrate the predictive validity of performance testing for real-life crash risk: 1) a lack of theoretical performance models integrating all aspects of the driving task, and 2) a lack of epidemiological data demonstrating a conclusive relation between drug use and traffic accidents. The former refers to the fact that investigators have never been able to truly define the basic components of the driving task and their underlying psychological and neuropharmacological principles. Instead, investigators have turned to the multi-faceted approach for measuring isolated skills in laboratory task, driving simulators or on-the-road driving. The latter refers to the fact that availability of reliable epidemiological surveys on drug-induced crash risk accelerates attempts to validate any kind of driving performance tests against a real-life occurrence, such as crash risk. To date however, epidemiological data on the association

between drug and crash risk are still very limited. Consequently, the construction of a well-founded task battery to evaluate drug effects on performance always has been, and still is, a major research priority.

Nevertheless, there are a number of performance tests with demonstrated sensitivity to both beneficial and detrimental drug effects on driving performance. Most notable is the standardized road tracking task [2] that is conducted on the road in normal traffic to measure lateral position control and which has been used in over 90 experimental studies to date. Some laboratory tests, measuring tracking ability, impulse control, and cognitive function have shown exceptional drug sensitivity as well. It is postulated here that it is also possible to establishing the reliability and validity of these tests for predicting crash risk by applying some basic psychometric principles.

Reliability

Test reliability covers several aspects of consistency. It indicates the extent to which differences in test scores are attributable to true differences in the characteristic under consideration or to change errors. The measurement of test-retest reliability is essentially simple. The scores from a set of subjects tested on two occasions are correlated. Test-retest correlations have been repeatedly calculated for the standardized, on-the-road driving test by comparing driving performance of subjects who completed the driving test on two occasions during placebo treatment. These analyses show that mean values of the dependant variable obtained during these driving tests (i.e. the standard deviation of lateral position, SDLP) were highly comparable among individual subjects. Consequently, test-retest correlations or reliability of the driving test have been shown to be very high (i.e. $r > 0.85$ [21]).

Test reliability is a valuable construct that should be relatively easy to calculate for any measure claimed to assess driving or skills related to driving.

Validity

A test is valid if it measures what it claims to measure [22]. The validity of a test, however, can be described from several angles.

Content validity

Content validity is concerned with a test's ability to include or represent all of the content or a representative sample of the behavior domain [23]. Content validity is usually a bottleneck problem when measuring driving or skills related to driving because a broadly accepted reference framework or model integrating all basic skills underlying the driving task is missing. To date, no single performance test exists that comprises all relevant aspects of the driving task. Even one the most accepted tests for measuring drug-induced driving impairment, i.e. the standardized

road tracking task as described above, validly measures only a part of the driving task and a part of total drug action. Likewise, laboratory tests usually assess single aspects of the driving task and none of them is capable of encompassing all the potential danger areas for the effects of drugs. Consequently, investigators have usually decided to include a wide range of laboratory tests comprising performance areas such as: motor control, decision making, risk taking, vigilance and attention, perception, among others. The final evidence that the drug in question would be safe or hazardous should subsequently be based on the combined results of laboratory tests, simulator tests and actual driving tests [24].

Predictive validity

Predictive validity is the ability of a measure to predict something it should theoretically be able to predict. A high correlation between changes in the measure and changes in the construct that it is designed to predict would provide good evidence for its predictive validity. Thus, in the field of experimental drugs and driving research, we should consider whether actual driving tests or laboratory tests of skills related to driving actually predict crash risk in real life.

The predictive validity of performance tests in drugs and driving research is usually unknown, primarily due to a lack of real-life epidemiological (crash risk) data in general. The absence of such data has made attempts to correlate laboratory data to real life driving accidents extremely difficult. However, it should also be noted that, in the past, investigators have often neglected to calculate the predictive validity of their performance tests for alcohol induced crash risk, even though a wealth of epidemiological data is available. This can be considered a major deficiency in experimental drugs and driving research, since any performance task with demonstrated predictive validity for alcohol induced crash risk is also likely to be sensitive to drug induced crash risk.

In the case of the standardized, on-the-road driving test, sufficient alcohol calibration data are available to calculate the relation between alcohol induced changes in SDLP and alcohol related crash risk as a function of blood alcohol concentration (BAC). It is noteworthy that both SDLP and crash risk rise exponentially with increasing BAC, and it thus comes as no surprise that alcohol induced changes in SDLP are highly correlated with alcohol induced changes in crash risk ($r = 0.99$). The conclusion is thus warranted that the validity of the road tracking task for predicting alcohol induced crash risk is very high (Fig. 1).

Recent epidemiological data on THC and BZD (benzodiazepine) induced crash risk also offer the opportunity to calculate the predictive validity of the driving test with respect to these drugs' potential for crash risk. Figure 2 demonstrates that diazepam-induced changes in SDLP do correlate highly with diazepam-induced crash risk as a function of time after dosing ($r = 0.97$).Together, these data demonstrate that the standard road tracking task is a very reliable predictor of alcohol and drug-induced crash risk.

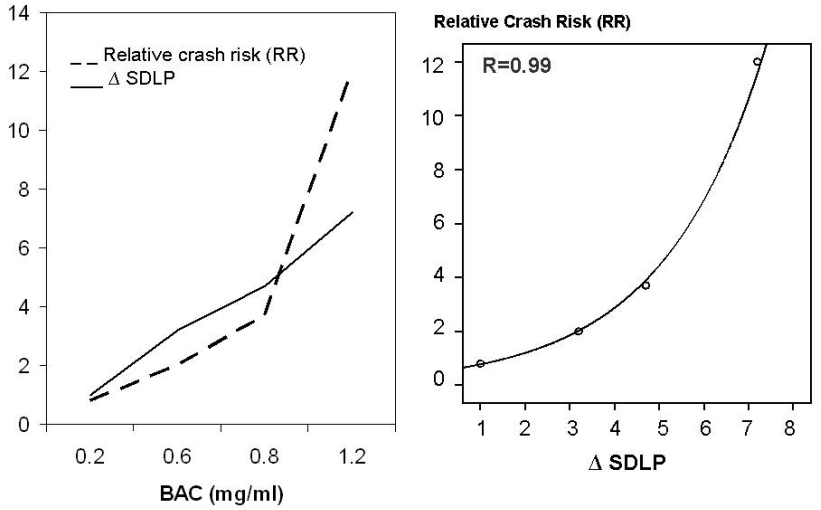

Figure 1 Curve fitting (right panel) of changes in SDLP (road tracking task) and relative crash risk as a function of blood alcohol concentration. SDLP and crash risk data were taken from Louwerens et al. [24] and Borkenstein [25].

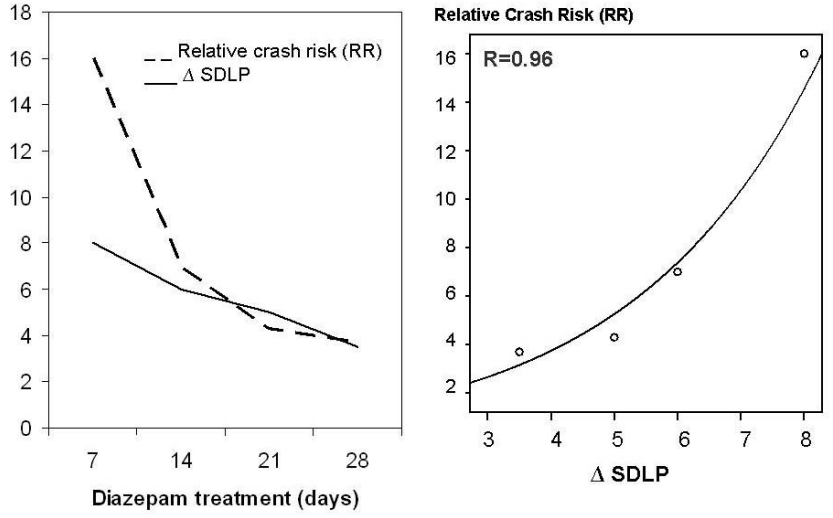

Figure 2 Curve fitting (right panel) of changes in SDLP (road tracking task) and relative crash risk as a function of blood alcohol concentration. SDLP and relative risk data were taken from Van Laar et al. [27] and Neutel [28].

Despite these impressive data on the predictive validity of the actual driving test, it should be recognised that the SDLP measures only partial aspects of the driving task, i.e. tracking ability and vigilance. Obviously these are keys aspects of driving that should never be neglected; however, other aspects of driving may be important as well.

External validity

External validity is related to generalising. External validity is the degree to which the conclusions from a study or measure would hold for other persons in other places and at other times. The issue is particularly relevant in studies assessing medicinal drug effects on driving, because these are usually conducted with healthy volunteers. It has been argued that patients do not experience side effects to the same degree as healthy volunteers. For example, most driving studies on the effect of antidepressants on actual driving performance have been conducted in healthy volunteers. It could be argued that healthy volunteers respond differently to antidepressant treatment than depressed patients and that one response does not predict the other. The obvious example is that depressed patients may respond favorably to antidepressant treatment, whereas healthy volunteers do not. Nevertheless, the rationale for studying antidepressant effects in healthy volunteers is that they experience side effects just like patients. This is certainly important at the beginning of depression therapy and in the minority of patients who do not respond to antidepressant treatment. It is assumed that somnolence or sedation is by far the most important cause of driver impairment in patients treated with antidepressant drugs. Regression analyses of elevations in SDLP observed in experimental driving studies, and the number of patients in clinical trials complaining of somnolence with the same antidepressants, strongly support this notion. Elevations in SDLP caused by antidepressants in healthy volunteer trials sharply increase as a linear function of the percentage of depressed patients complaining of somnolence in clinical trials ($r = 0.95$). These data thus indicate that the external validity of the actual driving test applied in a healthy volunteer model is very high [21].

Propositions

- Investigators should be able to justify the use of a performance test on the basis that it provides valid indices of a specified pharmacological effect and a specified mental/behavioral reaction relevant to driving.
- A test battery should measure as many of the relevant pharmacological aspects of a drug as possible, and as many of the mental and/or behavioral reactions of relevance to driving as possible.
- In general, performance measures used to define the effect of drugs on driving should posses a high test – retest reliability coefficient for raw scores measured in the absence of a drug effect (e.g. $r > 0.70$).

- Investigators should always fit experimental performance data with epidemiological crash risk data in order to define the reliability of a specific performance test for predicting drug-induced crash risk.
- Studies to show a drug effect on driving or skills related to driving should be designed to establish a dose-effect as well as a concentration-effect relation (i.e. multiple doses and quantification of drug concentration in blood)
- It is possible to attain results of practical relevance from studies employing healthy volunteers as subjects. This is not only the case when it is known or strongly suspected that healthy volunteers and ambulant patients experience different drug reactions capable of influencing their driving ability.
- Studies to establish the driving hazard potential of a particular drug should proceed from conventional laboratory testing to driving simulators and actual driving tests. The final evidence that the drug in question would be safe or hazardous should be based on the combined results of these tests [24].

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Measurement and methods to determine driving ability

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Abstract

To measure driving ability under the influence of drugs several scientific approaches are used: transfer of knowledge from other scientific disciplines and case reports, experimental studies like prospective controlled randomized trials and epidemiologic experimental studies, epidemiologic studies, e.g. cross-sectional studies and case-control studies, and systematic reviews and interviews. The methods are described, quality criteria are outlined and the advantages and disadvantages of experimental and epidemiologic studies are discussed.

Introduction

Modern life is characterized by mobility. At the same time the use of alcohol, the recreational use of illegal drugs or, especially in elderly people, the intake of prescribed medicines seem to be media of self-actualization for many people. Since alcohol, illegal drugs and medicines potentially have an impact on the individual performance, e.g. the dynamic performance capability, mobility and in particular traffic safety is affected. To ensure traffic safety under conditions of drug use, sound scientific and validated research methods are necessary to assess and measure the effect of drug use on driving ability. The more accurate the measuring of driving ability will be the more users of drugs will acknowledge the results of appropriate studies.

In the following we describe some specific details of different methods and study types, which are used to assess driving ability.

In general methods to measure driving ability can be arranged into four groups:

– transfer of knowledge from other science disciplines and case reports
– "experimental" studies: controlled randomized trials and (road) driving tests

– epidemiologic studies, e.g. cross-sectional studies and case-control studies etc.
– systematic reviews and interviews

As in many other areas of medical research, the main empirical methods are experimental or epidemiological studies.

In the following section we will briefly discuss these methods.[1] In general the quality of such a study has to be assessed with respect to many aspects like data interpretation or quality management. In a final paragraph we give a short perspective on future tasks of methodology. Our discussion is focused on the specific features of the general study types above, which have to be considered when driving ability has to be assessed [1–4].

Transfer of knowledge from other scientific disciplines and case reports

As for other scientific disciplines, for traffic sciences observations single-case studies and the transfer of knowledge from other disciplines into traffic sciences are the source of each research question. For instance, if pharmacological experience shows that benzodiazepines have a sedating effect, it can be assumed that the sedation will lead to a dangerous participation in road traffic. In this context not only expert opinions or pharmacological models are the initial point but also single cases or case series. Single cases are observations from one individual, e.g. having taken the drug just prior to the crash, leading to the conclusion that there might be some association. In contrast, if the suspicion results from a small sample of cases, the term case series is often applied. After such initial suspicions *via* observation or *via* transfer of knowledge a lot of questions concerning the measurement of driving ability emerge and cause scientific confirmation by different methods.

Measurement of driving ability by “experimental” studies

In this paragraph we arrange studies in which drugs are applied to subjects under controlled conditions and in which the subjects are subsequently tested for their driving ability at defined time points after ingestion of the drug.

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1 In our description the terms “drug” and “specimen” are often used. “Drugs” include alcohol, illegal drugs (cannabis, heroin etc.) and medicines. “Specimen” describes one of the substances blood, urine, saliva, breath or sweat.

Prospective controlled randomized trials in healthy subjects, prospective matched pairs studies in patients and epidemiologic cohort studies are examples of such studies.

Methodology

The goal of a prospective controlled randomized study is to test the hypothesis that a defined drug effects driving ability. Hence a sample of healthy subjects is tested with and without a defined drug in randomized order by a test battery (a number of performance and behaviour tests that represent driving ability).

A prospective controlled randomized study may demonstrate that the effect of a drug impairs driving ability. But this result does not necessarily imply that the user of a drug is not able to drive a car safely. By tolerance to the drug's impairing effects or, e.g. in patients, by positive effects of the medicine on performance-impairing effects of the disease it seems possible that performance under the effect of the drug is different in users compared to healthy subjects. Therefore a study in users/patients may be meaningful. Because it is impossible due to practical reasons to test all people taking a specific drug in an epidemiologic cohort study, the researcher selects a sample of subjects representative for the study population. If possible, he will choose a subject as its own control (acute users). If this is impossible, e.g. in patients with chronic diseases or drug-dependents, the researcher will select a control group not taking the drug that is as similar as possible to the patients. In general he will match each patient with a control regarding aspects like gender, age, education etc. All subjects have to complete the performance test battery.

In order to be able to interpret any differences of the results between "drug" and "no drug" in terms of driving ability in all the study types mentioned above, all other aspects influencing performance have to be eliminated. It is very difficult to realize these principles in an individual study. Many details concerning hypothesis and sample size, subjects, design and treatment, operationalization of driver fitness and the statistical evaluation have to be observed in order to ensure quality; they are discussed in chapter 9 and Appendix II.

Characteristics of experimental studies

Sytematically and adequately conducted "experimental" studies are important to understand the effect of the use of drugs on human performance and crash causation.

Obviously, like in most situations where it is assumed that an exposition has an effect on the occurrence of an event – for example the exposure to tobacco smoke and the occurrence of lung cancer – in the situation of exposition to drugs related to the occurrence of crashes, randomized experiments are impossible to perform because of ethical reasons. Thus epidemiologic studies are the primary empirical research methods to assess the effect of drug use on driving ability.

In comparison to epidemiological studies, "experimental" studies are characterized as follows:

– *Experimental studies can be designed to show very drug-specific effects in specific groups of users.*

It is possible to test particular subjects (young males or females, elderly people, drug-dependents, drugged drivers after rehabilitation, etc.) in their typical drug use behaviour (time, dose, environment, etc.) under other exploratory variables, which form the strata of the trial, at defined times after the use of the drug (resorption, time of maximum concentration, elimination, past elimination, etc.). By choosing special tests and ranking the level of difficulty, the performance tested can be selected according to any demand (type of participation in road traffic, being compensated/non-compensated by other performance, etc.). Finally the level of the drug effect can be measured by subjective ratings of the participants, by physical and psychological examination and by toxicological methods, to distinguish between subjective feeling and objective danger.

– *Experimental studies provide results even with rarely used drugs.*

They provide information about the effects of seldom used drugs, e.g. special medicaments with a low or very low exposition in real road traffic.

– *Results of experimental studies can be interpreted specifically for the drug under study.*

Since with an adequate trial design all influencing aspects on the test results are kept constant except the factor "test drug" and by consecutive prospective enrolment, the results is the strongest evidence on the cause effect relation.

– *Experimental studies measure a potential risk.*

The risks measured may not necessarily occur in real traffic situations. Statistical significance does not necessarily have practical relevance, i.e. a significant but small drug effect in experimental studies does not necessarily imply a relevant risk in real traffic. On the other hand the effect of a drug may be so severe that the user of the drug feels so impaired that he will abstain from driving.

– *Experimental studies can be misinterpreted because the experimental situation is rather artificial and not of practical relevance.*

An example is a performance test which discriminates even very small differences between substances, however, the performance tests mirrors the driving ability only partly.

– *One major drawback of experimental studies is the danger of overestimation of the drug effect in real traffic.*

As mentioned before, experimental studies are somewhat artificial, e.g. because of narrow inclusion and exclusion criteria. Thus the risk of crashes is difficult to assess and one would expect an overestimation of the danger in a practical setting. One reason is that subjects in experimental studies at most cannot compensate bad performance in a specific performance area by a better performance in an other performance type: e.g. slower reaction compensated by slower driving; bad performance in some performance areas compensated by choosing highways with smaller demands on reaction, lack of attention compensated by driving round instead of driving through a city (elderly people).

– *It is impossible to establish legal concentration limits by experimental studies.*

It is obvious that the results of an experimental study completely depend on the design, especially on the complexity of the test battery. For this reason and because of the fact that experimental studies only measure a potential, not a real risk, it is impossible to establish legal limits by experimental studies. A minimum prerequisite for this would be an internationally acclaimed standardized test battery representing "driving ability".

Measurement of driving ability by epidemiological studies

Different epidemiological study types exist which result in different conclusions, involving different types of error (bias) and with different limitations of interpretation. However, to assess the influence of drugs on driving ability, even the weaker methods like epidemiological studies compared to experiments are very important, because they can be used to describe the impact on the practical situation only.

In this section we discuss some epidemiological measures and study types and their special relation to the field of driving ability research.

In general epidemiological research aims at determining the frequency ("risk") and the conditions ("risk factors") of occurrence of safety-relevant events (descriptive epidemiology). In addition, the analysis of factors influencing the occurrence rates mentioned before (analytical epidemiology) are of interest in epidemiological research.

Obviously beside the study types used to answer a specific research question, the implementation of a study affects the quality of the results.

Methods

Prevalence, incidence

Descriptive epidemiology provides frequency measures of an event of interest, like crash frequency in a defined population. These measures can be used to compare populations. Prevalence and incidence are common and well-known measures to describe such frequencies.

Prevalence gives an estimate of the event probability, like crash frequency, in a population, like the population of car drivers. In principle prevalence will be given for a single time point (point prevalence), but due to practical reasons like documentation effort, prevalence is usually related to a time period (period prevalence). Most often the prevalence will be related to a year. In this case past crashes and newly occurred crashes in this time period are used for the estimate.

In contrast, incidence relates only to the new observed crashes within a small time period. It is rather a rate than a probability and can be used to assess the increase in the frequency of crashes per time unit. Under some special circumstances, the incidence can be used to approximate the prevalence.

Crucial for an accurate interpretation of these measured values are clear definitions of the characteristic (variable and its classification) and the reference population.

Cross-sectional studies

Crash surveys

The aim of a crash survey is to provide an estimate of the frequency of drug use in crash drivers. This estimate can be provided by identifying all crashes within a well-defined time period and looking if the corresponding drivers have taken a specific drug. This is a cross-sectional study in the epidemiological terminology.

Beside complete population of all crashes, samples were analysed in cross-sectional studies. In the ideal case in a crash survey, the sample consists of all drivers (independent of the suspicion if they are culpable or not) in a defined geographical area who are involved in a crash and who have been injured or killed. Specimens were taken from each driver and were analysed chemically-toxicologically for prior use of drugs. The frequency distribution of drugs then gives a first indication of the impairment of the drug on driving ability.

In general one cannot expect that the sample is representative for the totality of crashes due to many reasons: only road traffic situations with a crash, only crashes with damage to persons, not all drivers will be transferred to the study hospital or the institute of forensic science in the region, frequency and kind of crashes will depend on the study region (for example rural *versus* urban, small region with fast access to a hospital etc.). However, it may be possible to mirror the population under study within a subset of the sample.

Crash surveys cannot be performed in all countries, for instance due to legal regulations. In Germany, for example, it is not allowed to analyse blood of non-culpable drivers for drugs in a hospital without consent of the driver. Especially when a driver has indeed used drugs he will probably not agree with a toxicollogical analysis.

Road side surveys

The aim of the road side survey is to provide an overview of the drug use frequency in non-crash drivers. Hereby a representative sample of the population of drivers

is enrolled in the study to estimate the prevalence of persons exposed to drugs. To mirror the population of drives of a defined region, information about the distribution of drives in that region are necessary.

In contrast to the crash surveys the drug use is determined in the population of drivers who are actually crash-free. Consequently, a road side survey is a method to determine how often driving ability seems not to be impaired ("normal" traffic without a crash) by the drug. Moreover, as in crash surveys, because of practical restrictions, a sample is used to mirror the characteristics of the population under consideration. The sample consists of a representative selection of all drives in a defined region. From every driver who is incorporated in the sample a specimen is taken, and information on place and date of check and on the driver (health, demographic data, if applicable a physical examination for health and fitness to drive) is collected. Findings of the toxicological screening are added to the data set.

Two aspects are essential for a good road side survey and may be the major sources of bias: the representativeness of the sample for the entire volume of traffic and as few non-responders as possible. Usually drivers should be selected using a random mechanism, e.g. by dividing the population into clusters, like dividing the country under consideration into subregions, and to draw a random sample of the subregions rather than the drivers. In any case, in particular if a strict random sampling is impossible, the proportion of drug users related to non-crash drivers has to be adjusted for over- or underrepresented traffic conditions with regard to the region, place, time of the day, day of the week, age and gender of drivers etc.

The second major source of bias belongs to the non-responder rate, the number of people who refuse to participate in the survey. If the number of non-responders is high, the result is a less reliable estimate of the prevalence. This problem has a dramatic effect if the drug under consideration is used rarely, because no data about the use of the drug can be gathered in case of high non-responder rates. Obviously, the kind of extraction of the specimen, e.g. from saliva or serum has an effect on the non-responder rate.

It should also be recognized that there is no unique method to treat non-responders in the analysis stage of the study. Here, sensitivity analysis like worst case (all non-responders are treated as drug users) or best case (all non-responders are treated as non-drug users) analysis should be given. Confidence intervals should be included in the estimates to show the variability of the data. A detailed description of reasons for non-responding is necessary in order to assess the influence of the non-responder rate on the derived estimates (selection bias).

Comparison of crash surveys and road side surveys

First of all, it has to be recognized that crash surveys and on-the-road surveys differ with respect to the aim. However, crash surveys from different regions provide an estimate of the prevalence of drug use prior to a crash which can be compared with respect to different regions. Similar on-the-road surveys result in an estimate of the prevalence of drug use under non-crash drivers. To perform comparisons with

respect to regions, respesentative samples are necessary. In general the results cannot be combined.

If a drug is used rather seldom, the sample size of the road side survey has to be very large. However, if the drug is known to have a strong effect on driving ability, it could be expected that a large number of crash drivers belongs to this population. Then a crash survey is more efficient to show the association. As mentioned before, the selection of a representative sample is a major source of bias in both types of studies.

Case-control-studies, culpability analysis

Generally a case-control study starts evaluating all crashes in a defined region or a sample of these crashes. Then controls in crash-free traffic (one or several for each and every crash) are matched according to typical characteristics of crashes (e.g. location, time; gender, age, etc. of drivers). From all drivers of the two groups specimens are taken and a questionnaire (location, time etc. of the crash/drive; demographic data, health etc. of the driver; physical examination and fitness to drive) is completed. Data of the toxicological screening and, in case of estimating culpability risk, the classification into responsible and non-responsible drivers for the crash according to a decision protocol will round off the data set. The statistical analysis starts with an evaluation of potential sample differences, e.g. on the basis of heterogeneities in demographic factors.

One major drawback of this study type is that cases and controls are sampled from different populations. Thus there may be some other, probably unknown factors by which the populations differ and which support the association. Usually, these factors are called confounders and the effect on the association is termed confounder bias. Statistical methods to overcome such sources of bias are matching and stratification.

As a result of the study one distinguishes within the two groups of crash drivers and non-crash drivers:

- crash-drivers with a drug (C+), crash-drivers without a drug (C–) and
- crash-free drivers with a drug (F+), crash-free drivers without a drug (F–) then
- the relation of chances (C+:C–) : (F+:F–) is referred to as Odds Ratio (OR).

The OR is the ratio of the two odds (C+:C–) and (F+:F–), respectively. Each odds can be used to assess the fraction of drug users to non-drug users within the population of crash drivers or crash-free drivers, respectively. Thus the odds ratio describes how much more likely drug users are *vs*. non-drug users in the population of crash drivers as well as in the population of crash-free drivers. Formally, this measure is not a risk or risk ratio (relative risk). By definition OR is greater than zero.

An OR of 1 indicates that the use of a drug is equally likely in both groups, the crash drivers and crash-free drivers. An OR greater than 1 indicates that the use of a drug is more likely in the crash driver population, whereas an OR less than 1

indicates that the use of a drug is less likely in the crash driver population. Consequently, an OR of e.g. 2 for a defined drug in a culpability risk study means that the use of drugs (*vs*. non-use of drugs) is twice as likely in the population of drivers culpable for a crash than it is in the population of crash-free drivers. To assess the variability of the OR, a confidence interval should be given. Hereby, the confidence probability of 95 % is chosen. The meaning of the confidence interval is similar to a statistical test. A strong implication results if the confidence interval of the OR does not cover (the hypothesized value of) 1. Then, as already mentioned above, there is an association between the use of drugs and the crash driving. Obviously, if a drug is used rather seldom in the populations, the sample size to establish differences between the two populations must be rather high. Hence, concerning most of the illegal drugs and the medicines, it is almost impossible to establish the drug-driver association. Moreover, if one takes into account that several drugs are found in a single specimen (simultaneous use of drugs), the proof of the drug-driver association seems to be a complicated undertaking.

If the exposition to a drug in a population is high enough and allows a differentiation into concentration classes (e.g. alcohol), the ORs can be computed on the basis of C+, C–, F+, F– for the single classes. Hence the smoothened ORs of the ascending concentration classes form a hazard curve, in general a linear or exponential one, that starts with ORs slightly over 1 for very low concentrations and increases dramatically for very high concentrations.

It is very important to point out an essential fact for the interpretation of ORs: if there are too few cases to subdivide the concentrations of a drug the OR in principle represents the mean for all concentrations. But since in general the risk of a drug will increase with ascending concentrations, for low or high concentrations the risk may be completely different from the one given for the pooled sample.

A valid estimate of the pooled OR – independent of the concentration – will be given by stratified ORs, e.g. using Mantel Haenszel techniques.

Culpability analysis describes an approximation to case-control studies. Instead of taking a control group from crash-free traffic, the totality or a random sample of crashes in the study region is evaluated and the drivers are divided into culpable and non-culpable ones. To calculate ORs, the non-culpable drivers form the control group for the culpable drivers.

The advantage of culpability analysis is of course that the establishment of a control group from crash-free traffic is not necessary. The disadvantage of this approach is that it is often difficult to determine if a driver is only involved in a crash or is, at least partly, responsible for the crash. Thus some doubt might remain in an objective assessment of the culpability, especially in single-car crashes. As already mentioned above, confounders can bias the association here. For instance, the location, time etc. of culpable (cases) and the non culpable (control) crashes should be the same.

To get more homogeneous samples one can consider only multiple-car crashes differentiating between culpable and the non-culpable drivers. But even here some heterogeneity, e.g. from differently distributed demographic factors, cannot be ruled out and the question of culpability might be difficult to answer.

We know of no studies that try to elucidate exactly the consequences of the two different approaches (case-control studies and culpability studies) with respect to the interpretation of findings.

Pharmaco-epidemiological studies

As mentioned before, for methodological and economic reasons it is almost impossible to generate sufficiently large sample sizes concerning drugs seldom used. A so-called pharmaco-epidemiological approach tries to handle this disadvantage. Studies can be carried out for those substances the use of which is registered, e.g. medicines that have to be prescribed. The studies are based on two data sets: on the one hand patient-based data from defined prescribed medicines in a defined region and a defined period and on the other hand data of drivers involved in a crash or responsible for a crash out of crash registers and emergency rooms of hospitals in the same region and period. A comparison of the data sets provides figures of C+ and F+. If, in addition, a representative relevant control group without the drug is analysed even figures for C– and F– are established and ORs can be calculated. Caution should be given to the fact that the ORs may result from four different populations here, which intensifies the problems concerning bias mentioned for case-control studies.

A substantial disadvantage of pharmaco-epidemiological studies is the fact that it is not known whether a driver really took his medicine before the crash or if other influencing factors were the reason for the crash (e.g. additional use of other psychoactive substances).

Other epidemiological approaches, official statistics and other resources

There are other methodological approaches that are used to investigate the effect of drug use on driving ability: evaluation of protocols from policemen and physicians combined with the findings of toxicological screening of blood specimens taken from drivers suspected of driving under the influence of drugs; re-analyses of blood samples, i.e. additional toxicological screening of blood samples that are positive for alcohol; evaluation of documents concerning legal proceedings; etc. All these approaches are conducted without any knowledge about the subjects (social user, dependent, etc.) and about the cause of a potential impairment (drug, disease, fatigue, etc.). Due to further shortcomings, concerning heterogeneity of the sample as well as other aspects of the design, the interpretation of the results is very difficult or limited. However, to be positive, these studies may give some first hints on the drug effect.

Besides individual research projects mentioned before one will find official statistics in all civilized countries, concerning for example traffic volume and crashes. Especially crash registers can be helpful in measuring driving ability under the effects of drugs if they provide information about the use of drugs. It should be kept

in mind that most crash registers contain different information about crashes with respect to the characteristics of the damage, the number of injured or killed drivers and further influencing factors, e.g. between two classes of drugs, i.e. alcohol and "other drugs". For instance time series on alcohol-induced crashes may give a good view on the development within a defined country. However, due to the different kind and changes in documentation over the time, the comparison of numbers between different countries is of rather limited value.

Besides official statistics there is a lot of research that in fact does not measure driving ability under the effect of drugs but that helps to design an experimental or epidemiological study in particular with respect to representativeness. These "traffic-relevant databases" include background information on kind, frequency, habits (among other things: dose by a single period of use), gender and age pattern of the use of alcohol, illegal drugs and medicaments or frequency and habits of driving a car (times, driven distances, etc.).

Criteria influencing interpretation and quality of the results of epidemiologic studies

Methodological issues determine the quality of a study and consequently the interpretation of the results. An analysis of the limits of the interpretation is most often based on the possible sources of bias, like selection bias, confounder bias, information or misclassification bias, and so on. A comprehensive list of bias sources is given in [5]. A sound scientific description of the epidemiological study types mentioned before is given in [6].

A more detailed look at the methods shows that studies differ in design aspects like different regions, different drugs incorporated, differences in generating the sample size etc. and in the quality of carrying out the study. Hence many criteria should be taken into account when assessing the informational value and the quality of studies.

Describing the different approaches we already have pointed out some criteria that are important. In the following we compile some essential criteria. For an extensive list of quality criteria the interested reader may consider guidelines and recommendations concerning internationally acclaimed standards of epidemiological research [7] or special aspects of epidemiological research in road traffic [8, 9].

In general well-known considerations which have been formulated for randomized trials [10] can be applied to epidemiological studies as well. In brief, a well-defined research question, which corresponds to a statistical hypothesis described in a study protocol should be given. Herein ethical aspects should be considered which in particular show strong relations to statistical aspects like subjects, sample size and variables and to an internal quality assurance process. This process is based on data management, preparation, evaluation and protection, which affects the interpretation or generalizability of the study. Obviously, even the form of publication should follow international standards [11].

Characteristics of epidemiological studies

Epidemiological studies, in particular the road side surveys mentioned before, case-control studies and culpability analyses show, compared to experimental studies, some advantages and disadvantages.

– *Epidemiological studies cannot be designed to show drug-specific effects with highest evidence.*

In experimental studies it is possible to keep all factors constant at the design stage, so that – by randomization – the only influencing factor is drug use or not. Thus differences between the drug and non-drug group detected by the post-treatment measurement of a defined endpoint (result of a performance test) can be explained by the drug intake. This is not possible in epidemiological studies, where the influence of confounders cannot be excluded at all and these confounders may bias the results. So the scientific evidence for a drug effect is weaker. However, the good news is that the environment of the epidemiological studies reflects "normal life" better.

– *In contrast to experimental studies, epidemiological studies provide only results with frequently used drugs.*

The number of drugs that could be evaluated by the epidemiological approach is extremely limited due to the small exposition to drugs in road traffic in general. An evaluation of drugs that seldom emerge by appropriate study designs like long-lasting studies is difficult to realize from a methodological point of view due to change in toxicological screening methods, homogeneity of data, etc. Hence, today, solely alcohol is the substance that emerges frequently, enabling the calculation of concentration-dependent danger curves (ORs). Concerning cannabis and benzodiazepines, only few results exist up to now. However, it can be argued that a rarely taken drug in the population of drivers would cause a crash with a very small probability and thus does not play a practical role.

– *In contrast to experimental studies, epidemiological studies measure a real risk.*

Without doubt the essential advantage of epidemiology is that it represents reality, the samples are collected in real road traffic.

– *In epidemiological studies it is more likely to underestimate the danger of a specific drug.*

Because of possible heterogeneities between the study samples, it is more likely to overlook a possible drug effect. There are some methodological issues like matching or stratification, which can be used to minimize such heterogeneity, but it is well known from the literature [12] that the effects established from epidemiologi-

cal studies are pessimistic. The epidemiological approach underestimates risk: on the one hand because not all crashes are registered by the police (especially in rural regions because of missing information by drugged drivers or the time delay in arriving at the scene of a crash), on the other hand the careful behaviour of other drivers may avoid a crash.

– *In epidemiological studies it is possible to establish legal concentration limits.*

Epidemiological results can be used to establish concentration-dependent legal limits. As an example concerning alcohol, many studies exist which provide concentration-dependent ORs in form of a danger curve informing about the level of risk for each alcohol concentration. If traffic policy gives a limit in form of the highest, by the community accepted risk compared to sober drivers, by means of the danger curve the risk-related concentration can be calculated.

A fundamental problem with the interpretation of findings of epidemiological studies consists in a possible false conclusion about the cause-effect relation: the detection of a drug in a specimen of a driver does not necessary imply that the effect of the drug really is the cause of a crash. On the one hand the concentration of a drug may be so small that, *a priori*, an impairment by the drug cannot be expected. On the other hand even with concentrations in the "effective window" there may be other reasons for a wrongdoing like additional drugs not included in the toxicological screening, diseases, fatigue, etc. and even external reasons (weather, behaviour of other traffic participants etc.) may be of interest.

A second aspect concerning shortcomings in interpreting the results of epidemiologic studies is the fact that a separation between the effects of the drug and factors that are highly correlated with the use of a drug is not possible. For example often active, dynamic young men and women willing to take risks are users of illegal drugs like cannabis or amphetamines. Hence the question is whether the effect of the drug, or the personality of the driver is responsible for a risky driver operation characteristic (e.g. driving too fast). A drug-specific interpretation of the results is possible only by experimental studies (elimination of other influencing factors).

Systematic reviews and interviews

Meta-analyses

The need to make effective use of epidemiological and experimental research increases in importance as the literature rapidly increased over the last decades. Due to the diversity of the design of the studies it is impossible to summarize even the results of only a few studies by common reviews. An example are experimental studies on medicines: the published studies vary with respect to quality criteria (number of subjects, match criteria, control groups, level of statistical tests, etc.), dose of the medicine, time between use and the start of the performance tests,

number and complexity of performance tests, results and other variables. Hence, even if one selects only one substance, how should be compared, for example, the result of one study with 7 subjects that showed no significant (5% level) impairment in a reaction test 10 hours after the use of 10 mg diazepam with the finding of a second study on 20 subjects that demonstrates a significant (1%-level) impairment in an attention test 5 hours after the use of 5 mg diazepam? It goes without saying that every further study on diazepam will increase the complexity of results and the impossibility to interpret the results by a narrative review. What is required is a systematic structuring of the studies published testing the same substance and to integrate apparently different results.

In this regard meta-analyses that fulfil adequate quality criteria are the best approach to combine the results of published studies in order to effectively summarize their results. A standard to report the results of a meta-analysis is given by the QUOROM statement [13]. The standard – originally formulated for randomized controlled trials – can easily be applied to other study types. For more information see [14–16]. A very informative and helpful flowchart, guiding the researcher to conduct a meta-analysis is given in [17].

A meta-analysis has essential advantages compared to simple reviews of only a few studies. Information on driving ability can be based on many – if conditions are ideal, on all – relevant studies and part of the information can be quantified. Cross-tabulations of target variables with confounding variables as an example for basic statistical evaluation are possible. Rankings of performance areas in dependence of drug concentrations can be established, thus allowing comparisons between alcohol and illegal drugs.

Totalling meta-analyses are very informative instruments to measure driving ability. However, the assertion of the meta-analyis depends upon the quality of the aggregated individual studies. Thus the evaluation of the quality of the individual studies is a main goal of the work of meta-analysis.

Interviews in road users

Survey of drivers interviewed about their driving ability under the influence of drugs is one of the most frequently applied instruments. Special groups of drivers like young people, users of seldomly used drugs, drug-dependents, people with special diseases, etc. can be enrolled in such surveys. Besides questions concerning their driving ability (near-crashes, crashes, dangerous road traffic situation) under an influencing factor questions to learn something about the decision making to drive despite the use of a drug and further more interesting aspects (e.g. habits of using drugs) can be integrated.

The quality of an interview study can be evaluated by the following criteria:

- exact definition of the population under study
- sufficiently large representative random sample
- analysis of possible selection effects

– questions that are concentrated on the essential aspects of the study (experiences with drugs and fitness to drive) with unambiguous phrasing, using established validated scales
– efforts to control the validity of the answers by external information
– questioning by trained interviewers
– verification of the representativeness of the sample for the population under study by demographical data as the first step of statistical analysis of the questionnaire.

Face-to-face interviews provide more reliable information than interviews *via* phone or in written form. It should be noted that the consent to participate in the interview may depend on the fact that the data will not be handed to official institutions.

Perspectives

Today a broad spectrum of methods to measure driving ability under the influence of drugs is available and scientific disciplines like biometry, pharmacology, clinical research, etc. are perpetually engaged in developing improved and standardized methodologies.

Hence it would be desirable if the methods described above would be adequately realized in individual studies. Unfortunately there are many shortcomings even today. Screening the quality of published experimental studies only few studies fulfil all necessary requirements formulated in the ICADTS (International Council on Alcohol, Drugs and Traffic Safety) guidelines. For instance, most studies fail to provide arguments for an adequately chosen sample size. The representativeness or homogeneity of the subjects for the target population (especially in studies with medicaments) is questionable.

Treatments are not properly defined. Another problem concerns the correct formulation of the statistical hypotheses and the corresponding statistical tests, where tests for equivalence instead of the tests for significance should be considered.

Case-control studies or culpability studies are not frequently conducted and are difficult to compare due to the different designs. It would be of great value if a harmonization with at least a minimum amount of standardized variables could be achieved, thus making it possible to combine sample sizes and to calculate concentration-dependent ORs. Similarly the official statistics and the crash registers of different countries should be based on uniform definitions of criteria.

In many research questions a meaningful combination of different approaches would lead to better conclusions on the influence of drug effects on driving ability. An epidemiological study with inclusion of an interview with only a few questions, for example, would lead to a differentiation between patients using benzodiazepine and those dependent on illegal drugs who additionally use a benzodiazepine.

An important task of research in experimental studies could be the establishment of a minimum of standardized tests based on scientific evaluations that should be generally acclaimed and obligatory in experimental studies. Using such a test battery the comparability of studies could be improved and the pharmaceutical industry may be more interested in funding experimental studies.

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Simulator studies of drug-induced driving impairment

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Abstract

Driving simulators provide a safe means of identifying and comparing drug effects within a driver. While the scientific and societal benefits of driving simulators are numerous, the absence of a "standard" simulator has increased the difficulty of drawing conclusions across studies. This chapter compares the design of and results from driving simulators in substance abuse research from the past decade.

Simulators:

The National Advanced Driving Simulator is an elevated enclosed dome that houses an entire vehicle with full instrumentation and a 360-degree perspective. Its realism is unparalleled, but it is typically not used for substance abuse research. *The Advanced Mobile Operations Simulator (AMOS)* is sensitive to alcohol effects, but provides no outcome measures other than brake latency. *The AusED Driving Simulator* features a task design similar to that of the AMOS, but at a lower speed and at a different simulated time of day. It is particularly sensitive to sleepiness. *The University of Helsinki Driving Simulator* resembles the AMOS task in its brevity and limited number of dependent measures, and is sensitive to sedative drug effects. *The CyberCAR LITE* uses one large white screen rather than computer monitors. Highway and urban driving are simulated in day and night conditions. *The STISIM Drive* simulation allows for a longer, more realistic, and more interactive driving experience than the *AMOS*, and is sensitive to alcohol impairments.

Outcome measures:

Deviation from lateral position and reaction time have been increased by benzodiazepines and alcohol. *Vehicle Speed* has been characterized as insensitive to drug effects.

Future directions:

The standard measures of lane deviation, reaction time, and speed may be sufficient for identification of basic behavioral impairments. Yet other aspects of drug-related accidents – including manipulations of weather, time of day, traffic conditions, decision making, risk taking, divided attention, and sleep deprivation – deserve further study.

Nearly 40% of traffic deaths in the United States involve alcohol [1], and half of drivers who test positive for marijuana, cocaine, or opiates have elevated breath alcohol concentrations [2]. These findings illustrate the urgent need for improved understanding of the effects of alcohol and illicit drugs on driving. Driving simulators provide a safe means of identifying and comparing drug effects within a driver. The controlled nature of laboratory research isolates specific areas of driving impairment and the unique contributions of drugs and doses to those impairments. Consequently, the relative contributions to a collision of vehicle speeding, weaving, or delayed reaction time can be identified without any associated dangers to the driver.

While the scientific and societal benefits of driving simulators are numerous, the absence of a "standard" simulator has increased the difficulty of drawing conclusions across studies. Even when the same model of simulator is used by multiple laboratories, different measures within the simulator often are employed across studies. The ecological validity of simulated driving research is also directly affected by the realism inherent in each simulator. This chapter will compare frequently used and well known driving simulators in substance abuse research from the past decade. After a brief comparison of the most commonly quantified measures across studies, additional design elements that are infrequently incorporated but important for prediction of on-road driving performance will be discussed.

Noteworthy simulator models

The National Advanced Driving Simulator (NADS; [3–5]) at the University of Iowa was developed by the National Highway Traffic Safety Administration of the United States Department of Transportation. The NADS is an elevated enclosed dome that houses an entire vehicle with full instrumentation, including interactive steering and an operational dashboard. The simulator provides a 360-degree perspective for the driver. In one study of benzodiazepine effects [4], the NADS simulated a two-lane rural highway with minimal traffic. The task required driving "as you normally would" and culminated with the unexpected appearance of a truck into the lane of the participant's vehicle. Preventing the participant from changing lanes was another truck in the oncoming lane. While the realism of the NADS is unparalleled, its data have been presented in peer-reviewed substance abuse journals relatively less frequently than data from other simulators.

The Advanced Mobile Operations Simulator (*AMOS*; [6–10]), currently used to train police officers in Philadelphia, has been adapted for empirical measurement of brake reaction time. It is a partially enclosed chamber that includes a bucket seat, seat belt, steering wheel, dashboard, gearshift, and speedometer. Speakers located beneath the bucket seat provide sensations of a running engine, as well as squealing brakes, driving off the road, and colliding. Five connected monitor screens provide a 225-degree perspective. During the simulation, drivers are instructed to steer to keep the car in one line while maintaining a speed between 55 and 60 miles per

hour on a simulated highway with no additional traffic. At a random distance of up to 2.2 miles, a yellow barrier fence appears in the direct path of the vehicle. Participants are instructed to brake quickly in order to stop the vehicle and avoid hitting the fence. Latencies to release the gas pedal and to press the break after the appearance of the fence are averaged across 10 such trials. The AMOS has been employed for the direct comparison of effects of commonly used drugs. While its multiple screens and auditory stimuli provide some degree of ecological validity, its few outcome measures limit its practicality.

The AusED Driving Simulator ([11–13]) was designed primarily to identify impairments related to sleepiness, but also has identified interactions of sleep deprivation and alcohol intake. The simulator includes a computer monitor, steering wheel and pedals. The task design is similar to that of the AMOS, but at a lower speed and at a different time of day. Participants maintain a speed between 60–80 kilometers (37–50 miles per hour) on a rural road in a nighttime setting for 70 minutes. Periodically, trucks appear in front of the driver, and the driver must brake quickly to avoid hitting the truck. Because the truck appearances are separated by intervals of approximately 10 minutes, the task is sensitive to sleepiness.

The University of Helsinki Driving Simulator ([14]) is similar to the AMOS in its brevity and limited number of dependent measures. Driving time within this simulator typically does not exceed 10 minutes, and is as brief as three minutes [15–17]. The task, which is divided between day and night simulations, identifies the number of tracking errors and total time off the main course. The "severity" of impairment is operationally defined as the product of the errors and time off course. While the task may be comparably lacking in ecological validity relative to other simulators, it has proven sensitive to a variety of sedative effects in the presence and absence of alcohol.

The CyberCAR LITE [18] uses one large 175×120 cm (69×47 in.) white screen rather than one or more computer or other video monitors. On that screen is projected a road scene, including simulated dashboard with speedometer and mirrors, from the driver's perspective. A steering wheel and pedals are placed on and beneath a bench in front of the driver. The wheel mechanism includes a horn, ignition, gears, headlight switch, and hand brake. During the 20-minute simulation, highway and urban driving are simulated in both day and night conditions, and 34 possible errors are scored. Each error is weighted based on its perceived severity, with all scores ultimately summed. Sums are analyzed separately based on the time of day simulated, but across highway and city settings. An arbitrary cutpoint of 76 determines whether performance is "impaired".

STISIM Drive [19–22] is another personal computer-based interactive driving simulator designed to represent a range of psychomotor, divided attention, and cognitive tasks involved in driving. The overall simulation is fully interactive; the driver controls both speed and steering, with visual and auditory feedback provided. During the simulation, participants maintain a constant speed of 55 mph (89 km) in the right-hand lane of a winding road as in the AMOS studies. Unlike the AMOS studies, the STISIM task lasts for 20 minutes and nearly 19 miles with some additional

vehicles on the road. Collisions of any kind result in the appearance and sound of a shattered windshield, followed by the recommencement of the task at the collision location. Criteria assessed throughout the task include, but are not limited to, total number of collisions, total number of pedestrians hit, time-to-collision (a measure of tailgating), root mean square error around the speed limit, standard deviation of lane position, and total number of speed exceedances.

Like the AMOS and NADS, the STISIM can be used in a setting with increased realism. The most realistic STISIM arrangement is a vehicle cab with a 135-degree field of view [23]. However, the same STISIM software can be used in a less costly and less lavish setup that requires only a 19-inch computer monitor with no dashboard or vehicle chamber. The latter is relatively primitive in terms of realism. However, the extensive programmability and plethora of outcome measures of the STISIM have made it extremely useful in the alcohol literature and a promising inexpensive equipment option for the substance abuse field.

Outcome measures and their sensitivity to drug effects

Deviation from lateral position quantifies vehicle control by identifying the extent to which the vehicle diverges from a straight path. While some studies have defined the straight path as being centered within the lane, others have measured deviation from the driver's preferred lane position [4]. As side-to-side motions will result in increased deviation, a relatively high value typically indicates a vehicle that is weaving. Benzodiazepine hypnotic compounds, such as temazepam and zolpidem, have been associated with this impairment [17, 24]. Alcohol also has been associated with increased lane deviation [4, 11–13], particularly among participants with inferior baseline skill levels [19].

Vehicle Speed is quantified both independent of and in relation to identified speed limits. In some studies, speed limits are posted within the observed scenario. These speed limits may vary, and responsiveness of the driver to these changes is quantified. Surprisingly, while speed is frequently quantified, it has generally not been characterized as a variable sensitive to drug effects. For example, a review of psychotropic drug effects on simulated driving [25] identified multiple studies in which speed was unimpaired by benzodiazepines [26–28]. In other studies, speed is controlled by the investigators rather than used as a dependent measure (e.g. [6, 7, 9]). In the latter scenario, no speed limit signs are posted, but the driver is instructed to maintain a constant speed limit, typically 55 mph, in a highway simulation.

Reaction time is quantified in response to a novel, unexpected stimulus that typically requires the driver to apply the brake pedal. Such stimuli may appear within the simulation as a sudden image on the road in front of the driver [6] or as a standard red traffic light. Other stimuli, such as the image of a horn in a corner of the screen [29], may be independent of the road scenario. Reaction time has been particularly sensitive to the effects of alcohol [6, 7, 10, 30] and benzodiazepines [25]. Brake latency has also been slowed by marijuana ($p < 0.10$; [9]) to a degree comparable to that observed after a moderate dose of alcohol [6].

Future directions

As driving simulators improve in capabilities and realism, experimental designs must keep pace. The standard measures of lane deviation, speed, and reaction time may be sufficient for identification of basic behavioral impairments. Yet other aspects of drug-related accidents have been understudied. The breadth of knowledge obtained from simulated driving studies would be expanded with an increased focus on the following:

Vary weather, time of day, and traffic conditions

Driving simulations are typically tested under optimum conditions, including dry roads and daylight. The simulations, particularly in the AMOS and NADS, generally use highway scenarios. Yet drugs are used at all times of day, and drug-impaired driving occurs in rural and urban settings. While simulations should always maintain realism of the driving conditions, these conditions must reflect the most likely scenarios in which substances are used. Increased identification of the demographics of participants' drug use would help. For example, use of night time simulations among night time users, or controlled manipulation of traffic would improve our understanding of drug effects on driving beyond the nonspecific identification of slowed reaction time or impaired vehicle control.

Decision making and risk taking

While much focus has been placed on psychomotor impairments while driving, few studies have attempted to incorporate quantification of the decisions that precede such impairments. Even though the legal drinking breath alcohol limit is 0.08 % in the United States, doses that produce lower levels have consistently been associated with simulated driving impairment. A moderate dose of alcohol (0.5 g/kg) increased risk-taking and slowed brake reaction time in separate paradigms [6, 31]. Direct alcohol dosing impaired steering and braking; in contrast, expectation of alcohol had no significant effects on driving [30]. While alcohol expectancies (i.e., expecting then receiving alcohol) decreased risk taking, administration of alcohol when placebo was expected increased risk taking [32]. This finding suggests that risk taking might increase as a result of unexpectedly strong drinks.

Confounds from divided attention

Text messaging and smartphones are increasing in popularity and represent novel and dangerous distractions to drivers. As multitasking becomes easier for individuals, maintaining safety behind the wheel becomes more difficult. The combined requirements of reading and one-handed typing inherent in either text messaging or responding to an e-mail are beyond the scope of most prior studies of divided atten-

tion. Empirical studies of the consequences of mobile telephone use while driving have recently appeared, with slowed speed and quantifiable distraction among the observed effects [33, 34]. These studies focused solely on telephone conversation. The recent legislation in multiple states against text messaging while driving illustrates that conversations are not the only potentially dangerous use of a mobile telephone for a driver. The interactions of text messaging with drug use are a logical extension of current divided attention research.

Sleep deprivation

Partial sleep deprivation and alcohol have produced separate and combined impairments in measures of car following, steering deviation, lane deviation, and speed [12, 13, 35]. Driving was further impaired when alcohol was administered following *full* sleep deprivation [35]. While the effects of alcohol use following sleep deprivation have been reported, the effects of other drug use following sleep deprivation are less well understood. This is surprising because in addition to the effects of alcohol and benzodiazepines described above, the separate impairing effects on simulated driving of sleepiness [36–38], dexamphetamine [18], and polydrug use [39] have been identified. Given the high impact of sleep deprivation on motor vehicle collisions [40], further study of interactions of sleep deprivation and other frequently used compounds would increase the face validity of simulated driving research.

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The on-the-road driving test

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Abstract

The on-the-road driving test examines driving ability on a public highway in normal traffic. Driving performance is objectively measured by on-board computers. The combination of driving in real traffic, which gives the test high ecological validity, and objective measurement of driving performance makes the on-the-road test unique among other driving tests. This chapter discusses the methodology and background of the on-the-road driving test.

Subjects are instructed to drive with a steady lateral position within the right traffic lane while maintaining a constant speed. A camera on the roof of the car records the lateral position of the car. On board computers continuously record the lateral position and speed of the car. The Standard Deviation of Lateral Position (SDLP), i.e. the weaving of the car, is the primary parameter of the driving test. A secondary parameter of vehicle control is the standard deviation of speed.

During the past 25 years the on-the-road driving test has been applied successfully in psychopharmacological research, showing dose-dependent impairment for a variety of drugs including alcohol, antidepressants, hypnotics, anxiolytics, antihistamines and analgesics. Up to now, the on-the-road test has been acknowledged to be the gold standard method to determine drug effects on driving ability.

Introduction

Theoretical accounts making driving behavior understandable can be broadly divided into information processing models and motivational models. Motivational models are primarily concerned with the risks drivers are willing to take during driving, and include risk compensation models [1], risk threshold models [2], and risk-avoidance models [3]. According to motivational models, driving behavior is self-paced and determined by a cost–benefit analysis concerning the motives and

goals of the trip in relation to safety risks [4]. For example, people drive faster in an emergency, or adjust their speed under bad weather conditions. In other words, drivers adapt their driving behavior to their personal or environmental needs. As a result, these models are concerned mainly with risk taking, making them very popular in the field of traffic safety research. However, motivational models give little information about actual driving ability or driving-related skills. In contrast to motivational models of driving behavior, information processing models provide a functional analysis of the driver's task. For example, the model of Rasmussen [5] distinguishes three levels of cognitive control determining complex task performance, including skill-based behavior, rule-based behavior, and knowledge-based behavior. Skill-based behavior is largely automatic and effortless, routine driving (coordination between perception and motor actions), whereas rule-based behavior and knowledge-based behavior are controlled driving actions under new or unexpected circumstances. In rule-based behavior, drivers use prescribed actions (e.g., a passing maneuver) to deal with changed driving circumstances (e.g., a slower vehicle driving in front). If these rules turn out to be effective, behavior soon returns to the skill-based (automatic) level. If rule-based behavior is not sufficient, knowledge-based behavior is necessary, which implies conscious problem solving. Once the driver masters the unexpected or new situation, performance returns to rule-based or skill-based levels. The relationship between Rasmussen's levels of control is shown in Figure 1.

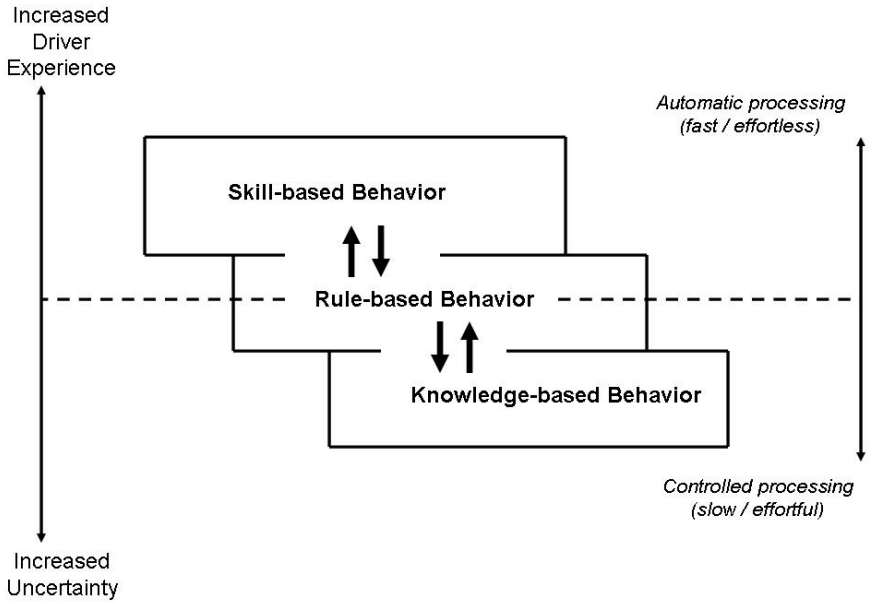

Figure 1 Automatic and controlled processing during driving.

Table 1 Driving behavior according to Michon and Rasmussen.

	Strategic/Navigational level (planning)	**Maneuvering/Tactical level (normal driving actions)**	**Operational/Control level (immediate vehicle control)**
Knowledge based behavior	Navigation in strange town	Controlling a skid on icy roads	Learner on a first lesson
Rule based behavior	Choice between familiar routes	Passing other cars	Driving an unfamiliar car
Skill based behavior	Home/Work travel	Negotiating familiar junctions	Road holding round corners

The distinction between automatic processing (fast and effortless) and controlled processing (slow and effortful) has been thoroughly described by Shiffrin and Schneider [6–7]. As indicated in Figure 1, a shift from automatic to controlled processing is made in case of increased uncertainty. The shift between automatic and controlled processing depends also on the driver's experience with a certain traffic situation. After repeated driving, several initially rule-based behaviors become skill-based behaviors as well. The concept of automatic *versus* controlled processing also applies to the theory posed by Michon [8], who suggested that driving behavior could be explained at a strategic level, a maneuvering level, and an operational level. Performance at the strategic (navigation) level is predominantly memory-driven, controlled processing, and concerns trip-planning, achievement of goals, etc. Performance at the maneuvering (tactical) level is environmental/data-driven, controlled processing, and includes normal driving procedures such as passing other cars, making curves while interacting with other traffic. Finally, the operational level is also data-driven, but automatic processing, and concerns immediate vehicle control, such as changing gears. Decisions made at the strategic level take minutes, those made the maneuvering level are made within seconds and at the operational level decisions are made within one second. The relationship between the models of Rasmussen and Michon is shown in Table 1.

It is evident from the examples in Table 1 that whether driving behavior is automatic or controlled depends on the driver's experience and the familiarity with the driving situation. In general, experienced drivers operate at the gray-scaled diagonal of Table 1, whereas novice drivers operate in the upper right corner of the Table.

Subjective driving assessments

Some research groups use subjective ratings of driving quality such as on-road scoring or using video recordings. The advantage of this method is that no expensive apparatus is needed to measure driving performance. Also, subjects can be tested in

their own cars. Unfortunately, research has shown that subjective ratings – either by experimenters, driving instructors, or the subjects themselves – are unreliable or do not adequately predict objective measures such as speed or SDLP [9]. The scoring methods varied from a simple pass-or-fail judgment to complex scoring of several skills and performances during driving. In has been demonstrated repeatedly that these subjective reports are inaccurate. Young drivers overestimate their driving ability and underestimate the risk of traffic accidents [10–11]. Cross-cultural differences in driver self-assessments have also been reported [12–13], and the accuracy of self-assessments is highly dependent on driving experience [14]. Nevertheless, approximately 80 % of all drivers report their driving abilities to be above average [15–16]. Other researchers concluded that drivers do not exaggerate their own driving skills and safety, but rather consider those of other drivers more negatively [17]. Also, psychoactive drugs may alter the awareness of reduced driving ability. Thus, it seems that subjects are not able to judge their own and others' driving ability accurately. Objective measurements of drowsy driving, such as alerting devices and EEG, are an improvement relative to the subjective measurements and are discussed elsewhere in this volume. Again, these measures – objective or subjective – record correlates to driving but do not predict actual changes in driving performance.

The on-the-road driving test during normal traffic

Up to now, the most accurate and direct way to measure driving ability has been the on-the-road driving test during normal traffic, developed in the nineteen eighties [18–19] and applied in over 50 studies with both healthy volunteers and patients.

In the 100-km driving test, subjects drive an instrumented vehicle over a 100-km highway track. In the right front seat, a licensed driving instructor accompanies the subject. His main job is to ensure safety during the driving test, and he is equipped with a brake and clutch system to intervene in the subject's driving actions, if necessary. If the subject or the driving instructor judges that it is unsafe to continue driving, the test is terminated before completion and the driving instructor transports the subject back to the Institute.

During the driving test, subjects are instructed to operate the instrumented vehicle at a constant speed and steady lateral position within the right (slower) traffic lane. A camera, mounted on the roof of the car, continuously records the actual position of the car within the traffic lane, by tracking the relative distance of the car from a delineated stripe in the middle of the road. Raw data collected during a driving test is shown in Figure 3. From this data the Standard Deviation of Lateral Position (SDLP), i.e. the amount of weaving of the car, is computed. Under placebo conditions, SDLP generally ranges between 10 and 30 cm, with a mean of about 20 cm. However, drug effects can produce an SDLP increment of 35 cm or more. SDLP is an excellent measure of vehicle control: with reduced control, SDLP increases (see Fig. 4). Excessive weaving may result in excursions out-of-lane onto both the road shoulder and the adjacent traffic lane. In this context, SDLP can also be regarded as a measure of traffic safety.

Figure 2 Measurement of lateral position.

Note that the camera for lateral position measurements is equipped with two infrared lights, to enable recording during the night and in dark weather circumstances. All data are continuously recorded on an on-board computer with a sampling rate of 2 Hz and edited off-line to remove data that were disturbed by extraneous events (e.g. passing, traffic jams, road maintenance). The experimenter, seated in the back of the car, monitors the on-board computer (reprinted with permision from reference [21])

A secondary parameter of the driving test giving insight in the amount of vehicle control is the Standard Deviation of Speed (SD Speed). Speed is measured from a pulse generator triggered by magnetic induction at a rate proportional to the revolutions of the drive wheels. Mean lateral position and speed are control parameters used to infer whether the subjects performed the driving test according to the given instructions.

Both SDLP and SD Speed are performance parameters measured at the operational/control level of driving performance. Under normal driving conditions, both lane keeping (expressed in SDLP) and speed control (expressed in SD Speed) are largely automatic processes, and examples of skill-based behavior, acquired through training and depending on the driver's experience. In the standardized driving test, subjects are instructed to drive at a constant speed and steady lateral position. This instruction involves planning at the strategic level, and changes motivational aspects and goals of driving during the test. However, while interacting with other traffic, subjects are sometimes unable to apply the instructions of the driving test.

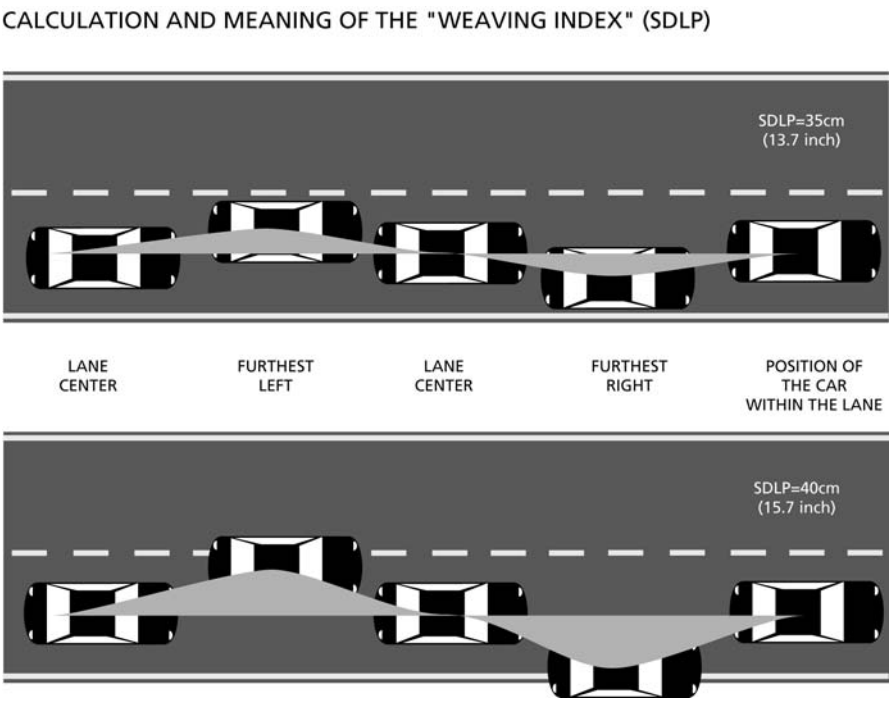

Figure 3 Standard Deviation of Lateral Position (SDLP).

Note that, with increasing SDLP, the weaving of the car becomes more pronounced, which eventually leads to out-of-lane crossings.

For example, sometimes speeding is necessary to pass a slower vehicle, or lateral position has to be changed to avoid an obstacle. These driving actions generally take place at the maneuvering level (but sometimes at the strategic level). The recordings from these driving actions are removed before analyzing the driving test data. It is, however, evident that both performance at the strategic and the maneuvering level will influence driving skills at the operational level (expressed in SDLP). The presence of other traffic and the occurrence of unexpected events, which are sometimes regarded as problematic, in fact are necessary components of the driving test. They are a prerequisite of its ecological validity that is often lacking in simple driving simulators and closed road tests.

Alcohol as historic control

One of the first studies using the on-the-road test examined the effects of different dosages of alcohol on driving performance [20]. Tests were performed on a 25-km

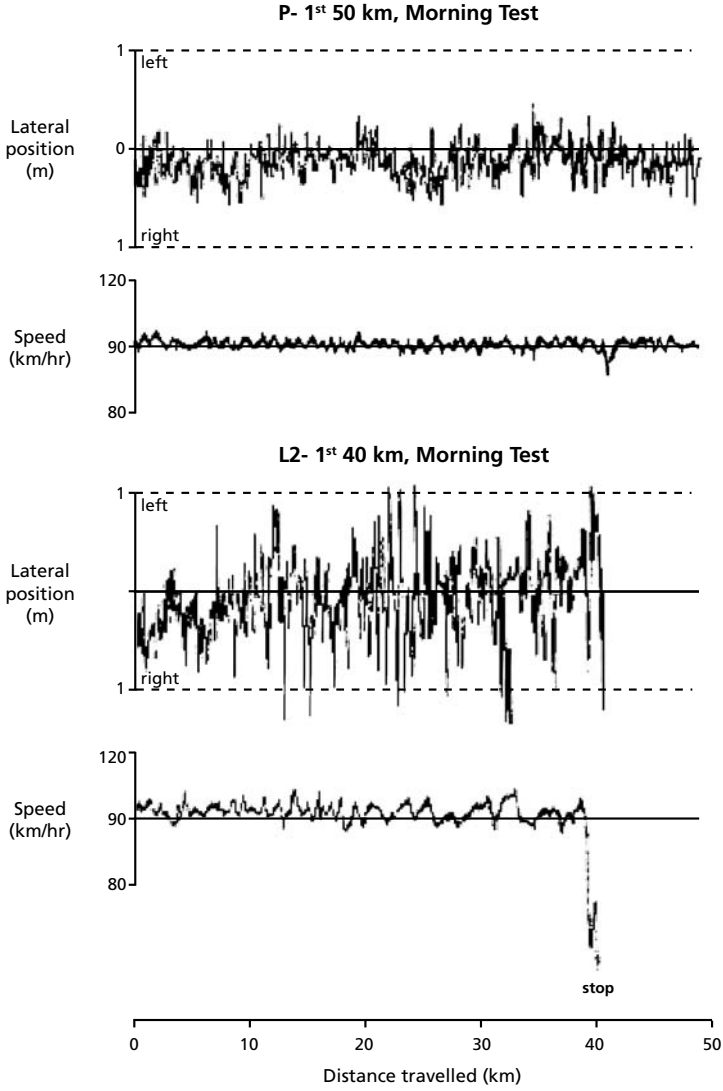

Figure 4 Example of raw data output for speed and lateral position.

Driving performance was measured in the morning following bedtime intake of placebo (P, top) or loprazolam 2 mg (L2, bottom). One meter left indicates crossing the lane boarder into the adjacent traffic lane; one meter into the right direction indicates crossing onto the road shoulder. The driving test in the loprazolam condition was stopped after 40 km due to repeated lane crossing (reprinted with permision from reference [21])

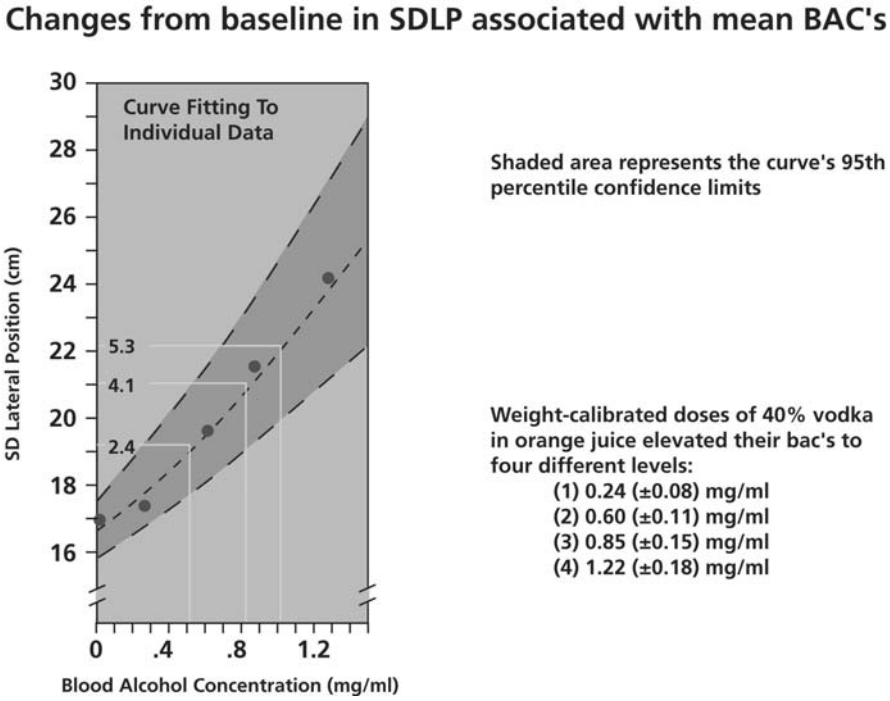

Figure 5 The relationship between blood alcohol concentration (BAC) and Standard Deviation of Lateral Position (SDLP). (Reprinted with permission from reference [22]).

closed road highway track, since Dutch traffic laws do not allow testing alcohol above a blood alcohol concentration (BAC) of 0.05%. SDLP was the primary parameter of the test. Results from different BAC levels are depicted in Figure 5. BAC levels of 0.05%, 0.08% and 0.10% correspond to the most common legal limits for driving a car. Many researchers who apply the on-the-road driving test use these SDLP increments (relative to placebo) to illustrate the magnitude of impairment observed with psychoactive drugs.

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Epidemiology and traffic safety: culpability studies

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Abstract

Scientific proof that drugs capable of impairing skills required for safe driving has only come relatively recently, although the proof for ethanol (alcohol) came almost 40 years earlier. Instrumental in obtaining this evidence has been the use of culpability studies. These have provided an epidemiological basis to demonstrate an increased risk for use of amphetamine-type stimulants, cocaine and for those drivers showing recent use of cannabis through the presence of THC greater 5 ng/mL in blood. Significant increases in risk (through odd's ratio analysis) using this form of study has not been demonstrated for opiates. Benzodiazepines has provided consistent increases in risk in this form of analysis mainly because they are usually associated with other drugs (including alcohol). However, alcohol–drug and impairing drug–drug combinations generally show a very high culpability rate and are usually higher than one impairing drug alone. Culpability studies complement case control and other types of epidemiological evidence that links, or attempts to link, recent drug use with a vehicular crash.

Introduction

Drug use is widespread in most Western-style communities for both legal and illicit drugs. Many of these drugs are capable of adversely affecting driving ability, none more so than those drugs subject to abuse. These include in particular the amphetamine-type stimulants (ATS), cocaine, cannabis in its various forms (particularly Δ^9-tetrahydrocannabinol or THC), benzodiazepines and related hypnotics and anxiolytics, and the opiate class of drugs.

While all of those drugs mentioned in the preceding sentence are capable of impairing key skills required for safe driving, proof that their use by drivers of motor vehicles leads to enhanced crash risk has been difficult to obtain until relatively recently. Conversely, it could be argued that drugs known to cause impairment of driving functions should be regarded as a road safety risk unless proven

otherwise. Nevertheless, it has become necessary in many jurisdictions to establish that drugs actually increase risk before governments actively enforce against their use in driving.

The difficulty in investigating the effect of drug use on driving has been caused by a lack of appropriate methodology to assess crash risk when a large number of factors are also operating to modify driver behavior generally and crash risk more particularly. The impact of alcohol was shown in the 1960s by the infamous "Grand Rapids" study [1], but the relatively low incidence of individual drugs in drivers limits the feasibility of such a case-control design. The number of cases required for statistical significance is much larger than corresponding alcohol studies, leading to prohibitive costs.

The design of a methodology based on an objective evaluation of culpability without knowledge of alcohol or drug involvement was conceived in the early 1980s [2, 3] and refined in the early 1990s [4]. Subsequently, this has led to a number of culpability-based studies in recent years to assess whether drugs are over-represented in drivers compared to control populations.

This chapter reviews those culpability-based studies and the evidence they provide on the involvement of alcohol and drugs on crash risk. Other chapters in this book cover other types of epidemiology studies and the evidence they provide on the role of alcohol and drugs on crash risk.

Design of culpability studies

In the context of road safety "culpability" is in reference to a person in whom few if any mitigating factors have been identified that take away his/her full responsibility for the crash, other than the variable being assessed. The variable is usually alcohol and/or drug use. This concept assumes that the culpability rate is sensitive to the effects of the presence of alcohol and/or drugs – providing, of course, that these substances do indeed increase crash risk. Is this were the case, then those drivers with alcohol and/or drugs present would show a higher culpability rate than drug-free drivers. Conversely, if a drug did not adversely affect driving skills one would not expect any change in the culpability rate.

In its simplest form researchers or crash investigators assess the circumstances of a crash and determine who was at fault [5–7]. In single vehicle crashes invariably the driver is seen to be at fault since there is no one else to blame.

More sophisticated methodologies grade the culpability from one to five or, indeed, some other series of gradations based on an assessment of a number of factors known to affect crash responsibility [2]. Further development of this approach used a structured questionnaire in which eight factors were considered in the evaluation of each crash, blind to the knowledge of whether alcohol or drugs were present in the driver [4]. These include adjustments to culpability based on vehicle roadworthiness, road and weather conditions, and the presence of fatigue. This approach is not based on any legal test, rather circumstantial factors that were operating at the

Table 1 Types of culpability analyses and their respective strengths and advantages.

	At fault assessment	**Graduated culpability scale**	**Semi-quantitative assessment of culpability**
Type or severity	Usually at fault or not at fault	Varying degrees of culpability assessed	Numerical score for culpability but usually dichotomized to 2 or 3 levels for statistical analyses
Strengths	Does not necessarily discriminate legal from circumstantial culpability[1]	Can more easily discriminate legal from circumstantial culpability	Can more easily discriminate legal from circumstantial culpability
Weaknesses	Relatively insensitive; requires a relatively large sample size; does not easily separate other factors associated with alcohol/drug use		

[1] These include road characteristics, weather conditions and roadworthiness of vehicle

time of the crash that may have contributed. For example, while driving a roadworthy vehicle is seen as the responsibility of the owner, the driver, even if s/he were the owner, could not have foreseen that the mechanical fault or bald tire would cause a particular crash (Table 1). This approach means that, in the right circumstances, drivers involved in single vehicle crashes can be found not culpable.

The drug-free driver is used as the control and provides the baseline culpability rate. This technique is quite good at examining retrospective records providing, of course, that the records allow most, if not all of the factors important to crash causation to be assessed and there is no selection bias.

The design of this form of culpability assessment gives points to each of a number of possible factors covering the eight areas. A culpability score is derived by summing these points. Drivers are allocated into one of three categories. The minimum score of 8 (to a maximum of 12) indicates full or almost full responsibility since there no (or few) mitigating factors. A score of 13–15 indicates that at least two of the factors were identified as taking away full responsibility. This contributory group is not used in the statistical calculations. Scores of beyond 15 indicate that a number of mitigating factors apply to the driver and put the driver into a "not culpable" category. The allocation of certain scores to one of the three groups was validated by researchers as providing the best allocation of drivers into the "culpable" and "not culpable" categories.

In practice there is little evidence that any one of these three broad approaches to the assessment of culpability materially affects the outcomes, providing the sample size is sufficient.

In this approach statistical analyses are conducted using odds ratio (OR) by comparing the culpability rates of drug positive and drug negative drivers. The following formula is used in such calculations.

$$OR = pC_T / pC_C \quad \text{eq. 1}$$

Where pC_T is the proportion culpable of the test group) (drug group) and pC_C is the proportion culpable of the control group (drug negative drivers).

Robertson & Drummer modified this approach further by calculating a culpability ratio at which the proportion of drivers in the various groups (i.e. drug positive or drug negative) were culpable (ratio of those culpable to not culpable). The odds ratio was the ratio of the culpability factors for the treatment group over the control group [4].

$$OR = CR_T / CR_C \quad \text{eq. 2}$$

Where CR_T is the culpability ratio of the test group (drug group) and CR_C is the culpability ratio of the control group (drug negative drivers), and CR = ratio of drivers culpable over those not culpable in a particular test or control group.

Whatever technique was used, statistical adjustments are required to account for variations in culpability due to age, gender, type of crash, time of day etc. [4, 8]. For example, it has been shown that the age of the driver affects driver culpability rates, with the middle aged driver showing the lowest rate [9]. Hence, if a drug positive driver group were much younger than the control group (i.e. cannabis users) then a greater drug effect would be seen than if an age correction were not conducted in the analyses. Logistic regression has typically been used to accommodate these statistical requirements.

Selection bias is always a concern. This could be caused by crash investigators tending to focus more attention on multiple vehicle collisions, since these often result in trauma to more persons, and the possibility of the offending driver being charged. In some jurisdictions alcohol or drug testing is not mandatory in all crashes involving serious or fatal injuries. When this occurs cases are selected for drug testing when drug use might be suspected. This results in an unrepresentative sample population.

Alcohol

Ethanol (alcohol) is clearly the most significant substance used by drivers (and other road users). The pivotal Borkenstein "Grand Rapids" study in the 1960s provided the foundation for epidemiological proof of the association between alcohol and crash risk [1]. Moreover, it clearly demonstrated for the first time that increasing crash risk was associated with rising blood alcohol concentration (BAC).

Culpability studies have since been used to verify this observation, or perhaps more accurately to verify the culpability approach to crash risk determination.

Injured alcohol positive drivers admitted to trauma centers have a significantly higher crash culpability than alcohol negative subjects [10] and is consistent with other studies assessing crash culpability in injured drivers [11–14]. Alcohol posi-

tive drivers who were either injured or killed were more often judged to be responsible for the crash than negative drivers [5]. Alcohol positive drivers "at fault" have twice as many crashes per 100 driver years than control "at fault" drivers [7].

Five years of hospital and crash data showed that the youngest and oldest drivers were more likely to have caused their crash and women drivers had a significantly higher odds of culpability at the highest BAC levels [15].

An assessment of hospital admissions showed greater injury severity and culpability was associated with a positive BAC [16]. The culpability was higher in drink drivers who had crashed compared with sober drivers [17].

Studies using the method of Drummer & Robertson [4] have shown a concentration-dependent increase in the proportion of drivers culpable with rising BAC [4, 9, 12]. Odds ratios of 2500 injured drivers admitted to hospital were 1.9 (under 0.05 g/100 ml) to 23 for those with BAC greater than 0.15 g/100ml. The culpability rate for alcohol positive drivers was 90 % compared to 53 % for drug negative drivers. Expectedly, this rate was highest for single vehicle crashes (96 %). An analysis of over 3000 fatally-injured drivers in Australia showed similar data, although significance was only attained at concentrations above 0.05 g/100 ml [4, 9]. At BACs in excess of 0.20 g/100 ml there was almost no driver who was not culpable. Graphical representation of culpability (as OR) with rising BAC shows very similar trends to those demonstrated in the Borkenstein study [1] (Fig. 1).

While some of the earlier studies may not have had a full toxicological workup compared to present day situations, studies have shown that alcohol effects are retained even in the presence of other (impairing) drugs [9, 12].

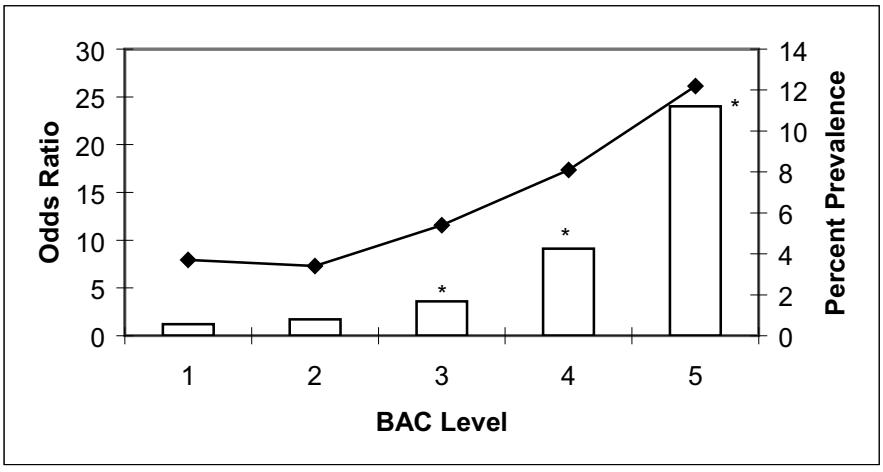

Figure 1 Odds ratio (bars) and prevalence of the blood alcohol concentrations (BAC) at five ordinal categories. (1 = 0.010–0.049 %, 2 = 0.050–0.099 %, 3 = 0.100–0.149 %, 4 = 0.150–0.199 %, 5 ≥ 0.200 %). *P < 0.05. Reproduced with permission [9].

All in all these studies verify that culpability analyses provide similar results to other forms of crash risk assessment and are therefore likely to provide useful crash risk data for drugs other than alcohol.

Drugs other than alcohol

The involvement, if any, of drugs on crash risk was not researched with any vigor until the 1980s, even though researchers had already recognized the impairing potential of many drugs used at that time. This was primarily because drug use in the community did not rise sufficiently to compete with alcohol-based trauma until about this time and, perhaps more importantly, the methodology available to assess drug-associated road trauma lagged behind that of alcohol.

One of the first papers designed to investigate the role of drugs on road trauma used a form of culpability analysis based on the method of Terhune [3]. This paper suggested a role for cannabis in increasing driver culpability. This was followed by another study based in California that did not show any increased culpability for drivers positive for cannabis (as THC) [18]. However, it was a small study of young male drivers who already had a much higher culpability rate than drivers across all age groups.

The culpability method of Robertson & Drummer has since been applied to a number of studies around the world to assess the role of drugs on crash risk.

Amphetamine-type stimulants (ATS)

This group of drugs includes the prototype amphetamine as well as methamphetamine and the designer stimulants, ecstasy (MDMA), MDA, MDE, MBDB etc. and, in some circumstances, other stimulants, such as the ephedrines, are included in this list [19, 20].

In the context of road safety, use of ATS have always been regarded as a potential risk, particularly for long distance truck drivers striving to keep awake during long, monotonous driving. In an attempt to ascertain the role of such drugs in 168 truckers, culpability of drivers killed in a crash (in the USA) was determined by an expert panel of toxicologists. This study suggested that amphetamines were overrepresented in culpable drivers [21].

In the Longo injured driver study there was a trend to increased OR (χ^2 1.6); however, there was no significant difference in the proportion of culpable driver across stimulant groups. The number of stimulant positive drivers was very small (n = 20) [12]. The French study on injured drivers again showed a trend to higher culpability for amphetamine users but this was not significant (adjusted OR 1.96) [22].

In the Australian culpability study ATS were found in 4.1 % of all fatally-injured drivers but 23 % of truck drivers [9]. Strong associations for culpability were seen for these truckers. The OR for truckers was almost nine.

Other studies using different methodologies have found an increased rate of impaired driving in amphetamine users [23, 24] and the over-representation of amphetamine users in crashes [25, 26].

Benzodiazepines

Benzodiazepines represent a large family of sedative drugs used in the treatment of sleep disorders, anxiety, and other applications such as in the treatment of epilepsy or use as muscle relaxants.

Longo and co-authors in a study of 2500 injured drivers admitted to hospital in South Australia found some evidence for an increased OR for drivers positive for benzodiazepines [12]. This was significant for drivers with concentrations at the therapeutic (OR 3.3) or supra-therapeutic concentrations (OR 3.6) (Table 2). The culpability rate increased further with alcohol or other drug combinations. Unfortunately, there was no correction for benzodiazepines administered post-crash as part of emergency treatment. This is likely to be a significant proportion of cases and would be expected to dilute any increase in OR caused by this class of drugs, since the drivers not responsible for the crash are just as likely to be treated as those judged responsible.

The Australian culpability study involved a series of studies spanning 10 years in three states and included almost 3400 fatally-injured drivers. Benzodiazepines not administered post-crash were detected in 4.1 % of the study population, but only one-quarter of these occurred in the absence of other drugs. The corrected OR (1.3) was not statistically significant (95 % CI range 0.5–3.3). The low OR was not surprising since very few of these cases had concentrations of benzodiazepines detected that exceeded those normally expected for therapeutic use.

The results from other epidemiological studies in regard to benzodiazepines and accident risk tend to suggest that they increase crash risk, although not all studies have shown an increase [27–34].

Cannabis

Cannabis (or marijuana) contains as the active substance Δ^9-tetrahydrocannabinol (THC) and is taken primarily through the lungs by smoking joints or the use of water pipes (bongs). Less commonly, cannabis material is taken orally by consumption of cannabis-containing biscuits (cookies) or such, in which the crude cannabis is activated by heat to release THC. This substance causes euphoria and a sense of relaxation and significantly reduces cognitive and psychomotor functions [35, 36]. These include divided attention skills.

There have been a number of culpability studies that investigated the association between cannabis and traffic crashes.

Early culpability studies using the method of Terhune were inconclusive on the role of cannabis on crash culpability [3, 18]. This could have been due to the

selection of the population and the small sample sizes, but may have been more related to detection of the carboxy metabolite of THC (cTHC) rather than the active THC in blood in some of the studies [35]. cTHC persists in blood some hours to days after last use of cannabis and is not biologically active [35]. THC is the main active substance and, if detected in blood above concentrations of about 2 ng/ml, suggests relatively recent use [37].

Hence it was not surprising that culpability studies using the measurement of cTHC as an indicator of exposure have not lead to the indication of increased crash risk [10, 13, 38]. In the Colorado study urine was used to assess cannabis exposure [13]. Similarly, in the Maryland study urine was used as the indicator of marijuana use [10]. cTHC can persist in urine for days or weeks after last use and cannot be used as an indicator of recent exposure at a time when impairment is likely [39].

In the South Australian injured driver study THC was measured in blood. Those THC concentrations above 2 ng/ml tended to show an increased rate of culpability, but the number of cases was small. However, since these specimens were obtained on average 2.7 hours after the collision [40] it is probable that most of the THC originally present had largely disappeared as a result of the short apparent elimination half-life of THC in blood (< 1 h).

The larger Australian culpability study in fatally-injured drivers showed that there was a statistically significant increase in culpability for drivers with THC in blood [8]. This increase was only apparent at blood concentrations above 5 ng/ml. The median THC concentration was 10 ng/ml with a range from 1–100 ng/ml. THC positive cases at any concentration showed a corrected OR 2.7 compared to drug free drivers (interactions for age, gender, crash type, jurisdiction, and year of collection were taken into consideration). Drivers in whom THC concentrations were at or above 5 ng/ml showed an OR 6.6 as compared to drug free cases. Indeed, blood THC concentrations below 5 ng/ml gave an OR of 0.7, indicating that this approach showed no increase in culpability until the blood concentration exceeded 5 ng/ml [41]. Further analysis of these data showed a concentration dependence at higher doses, i.e. that OR increased further as the THC concentration in drivers increased [41]. These data suggest that crash risk associated with higher concentrations of THC approach or even exceed the crash risk associated with alcohol at 0.15 g/100 ml.

Further statistical analyses of the data using polynomial functions show that blood THC concentrations are not associated with an elevated risk (OR > 1) until they exceed about 6 ng/ml (Fig. 2) [41]. This is equivalent to a serum THC concentration of about 12 to 16 ng/ml.

One of the tests for any epidemiological method is that crash risk should not be increased for drugs that do not impair. This was demonstrated in the Australian fatal driver study, since cases negative to THC but positive to cTHC in blood did not show an increase in culpability rate (OR 0.7) [9].

Laumon and coworkers used the culpability methodology of the previous study in over 10 000 injured drivers in France [22]. Control injured drivers were those considered not to be at fault. Their data also showed that cannabis use was associated with a concentration-dependent increase in culpability. The corrected OR

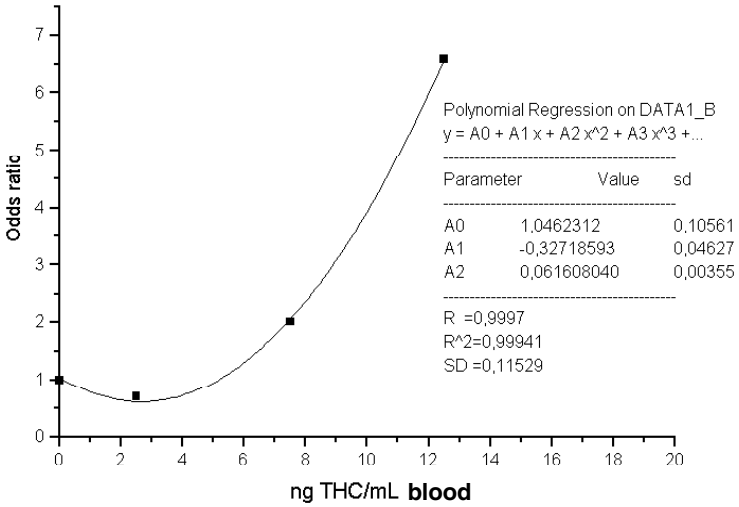

Figure 2 Correlation between THC concentration in whole blood and accident risk (odds ratio) calculated with data from the study by Drummer et al. (2004) [9]. Reproduced with permission from [41].

(adjusted for confounding factors) increased slightly at blood THC concentrations between 1 and 2 ng/ml (OR = 1.5, CI = 1.1–2.2). At THC concentrations >2 ng/ml OR increased to 2.1. These data provided further support that recent use of cannabis as reflected by positive THC in blood increases crash risk. In this study the delay from crash to sampling would again underestimate the actual THC concentration present at the time of the crash, since many of the blood samples were collected three or four hours after the collision. This could also explain the relative weak concentration risk response.

Other types of culpability studies also confirm that cannabis use is linked to increased crash risk. The historical cohort study in Ontario examined the driving records of 411 persons beginning treatment at a drug treatment center [7]. "At fault" drivers using cannabis were more likely to be culpable than control drug-free drivers (95% CI 1.2–2.3). Another study examined a large database of fatally-injured drivers in the USA [42]. Culpability was crudely estimated based on the available limited data on driving related factors listed for each case. The OR adjusted for age, gender, and driving record was 1.29 (99% CI 1.1–1.5); however, no concentration dependence could be assessed since such data was not available in the database. It is also likely that the database entries are not truly representative, since the prevalence of THC was higher than expected [42].

Table 2 Summary of reported OR of becoming involved in serious crashes (injured or fatally-injured) when impairing drugs are present as reported in culpability studies.

Substance	Odds ratio (range with median in parentheses)	References
Drug free cases	1.0	
Alcohol (BAC > 0)	8.5, 6.0	[9, 22]
Cannabis		
cTHC (no THC measured or detected)	0.2–2.1 [0.7]	[3, 9–13, 18, 38]
THC (blood/serum)	2.7	[9, 12, 22]
Alcohol/THC or cTHC	3.5–12 [8.4]	[11–13, 18, 38]
Opiates/opioids	1.4	[9]
Benzodiazepines	1.3, 3.4	[9, 43]
Stimulants (includes ATS, cocaine, and ephedrines)	2.0–4.2 [2.3]	[9, 22]
Any drug combinations	1.8	[9]

ATS = amphetamine-type stimulants, BAC = blood alcohol concentration, THC = Δ^9-tetrahydrocannabinol, cTHC = 11-carboxy metabolite of THC

Cocaine

There has been relatively little research using culpability analyses to investigate the role of cocaine. This is largely due to the more restricted distribution of the drug to certain localities compared to other drug groups and that, often, drivers use other impairing drugs [3, 13].

Nevertheless, cocaine, like the ATS, can demonstrate short term improvements in cognitive function; however, prolonged use leads to reduced performance [44, 45]. This occurs through adverse effects on divided attention tasks, increased risk taking, and hypersomnolence associated with fatigue.

In the study by Williams the cohort was a young male population in California in which 11 % of killed drivers had used cocaine recently. The small sample size and overall higher culpability rate of this group precluded sufficient statistical power [18].

In a study centered in Baltimore, cocaine using drivers (3.8 %) were associated with a significantly increase culpability for drivers 21 to 40 years of age [10]. This was also seen in a Canadian study in which cocaine was over-represented in “at fault” crashes [7].

Opiates

Opiates include those analgesics related to morphine, such as oxycodone, hydromorphone, hydrocodone as well as synthetic analogs that act like morphine (on the opiate receptors), methadone, meperidine (pethidine), fentanyl, etc. The illicit drug heroin (diacetylmorphine) is included here. Some of the less potent opiates that are often used for more general pain relief (treatment of mild to moderate pain) are also included here since their misuse will give morphine-like effects. These include codeine, dihydrocodeine, ethylmorphine, etc.

There is less epidemiological evidence accrued for this class of drugs even though they are commonly used and are capable of adversely affecting driving. As depressants of the central nervous system they are more likely to cause sleepiness and increase the manifestations of fatigue.

In the Australian culpability study opiates represented 4.9% of cases but only 1.7% involved no other impairing drug [9]. There was no over-representation in these cases compared to control drug-free drivers (OR 1.4, 95% CI 0.7–2.9). Similar negative risk findings were obtained in the French study of injured drivers (OR 0.9, 95% CI 0.6 to 1.5) [22].

In contrast, a case control study in France comparing the incidence of morphine in 900 drivers admitted to hospital from a car crash compared to 900 other subjects admitted to hospital for other reasons showed an OR 8.2 (95% CI 2.5–27) [46]. Another study of injured drivers (cars and vans) using randomly selected drivers not involved in a collision (as controls) gave a much lower OR (2.35) that was not statistically significant [47].

Drug combinations with and without alcohol

Alcohol is commonly associated with drug positive cases amounting to a quarter to half of all drug positive cases [48]. It is a common substance co-associated with cannabis, but is also associated with the other abused drugs.

The combined effect of THC and alcohol ($\geq$0.05 g/100 ml) reveal a significant increase in crash risk over THC alone (OR 2.9; 95% CI: 1.1–7.7) suggesting that THC enhances alcohol-induced impairment, and that this impairment is additive to alcohol [8].

There were insufficient cases in the other studies to properly examine the effects of the combination of alcohol and cannabis, although there was a tendency for culpability to increase when an impairing drug was present with alcohol [3, 11, 12, 18]. It be should pointed out that, in most cases, the effects of alcohol tend to predominate when the BAC is at or over 0.15 g/100 ml.

Drivers with combinations of impairing drugs are invariably more likely to be culpable than those using one drug alone [9, 12]. These combinations include benzodiazepines plus opiates, or cannabis plus amphetamines. This observation is not

unexpected, given that the more impairing substance present, the more likely is obtaining an elevated crash risk. Interestingly, one study showed that persons using cannabis and cocaine together had a reduced risk over either drug taken alone [7]. This observation has not been repeated but it may relate to the cohort being studied, since all were in treatment for their drug addiction.

Conclusions

There have been a number of epidemiological studies based on assessment of driver culpability. Those examining alcohol have replicated the general observations made by case control studies that alcohol increases crash risk, particularly those BACs over 0.10 g/100 ml. Studies involving hospitalized or fatally-injured drivers have generally shown that drivers with detectable blood THC concentrations are associated with increased risk, particularly those over 5 ng/ml. Significant increases in OR using this form of study has also been seen for cocaine and ATS, but not for opiates or benzodiazepines. Alcohol–drug and impairing drug–drug combinations generally show a very high culpability rate that is usually higher than for one drug alone. Culpability studies complement case control and other types of epidemiological evidence that links, or attempts to link, recent drug use with a vehicular crash.

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Case-control studies

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Abstract

The case-control design is very suitable when dealing with rare diseases and when many factors for the disease under study need to be evaluated, as is the case in determining the risk of driving under the influence of drugs. However, the methodology is hard to implement and there are many sources of potential bias that could affect the validity of the study results. Case-control studies are therefore not commonly used as a method to assess the risk of driving under the influence of psychoactive substances other than alcohol.

The few studies that have been conducted vary in study design, which makes it very hard to compare their outcomes. In 2006 a consensus meeting was organised by the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) to develop standards for future research. These recommendations for standardized research include legal/ethical issues, subject and study design issues, and core data parameters.

Introduction

Epidemiological case-control studies are regarded as the optimal methodological approach to determine crash and injury risks associated with driving under the influence of psychoactive substances, including alcohol, illegal drugs, and medicines [1]. However, most case-control studies have been conducted to determine the relative risk of driving under the influence of alcohol. The most cited study in this field is the Grand Rapids study by Borkenstein [2], conducted in 1964, that estimated drivers' crash risk at various blood alcohol concentration (BAC) levels.

Few case-control studies of drug driving have been conducted to date, since these studies tend to be very expensive and time (and labour) consuming. Furthermore, case-control studies are exposed to various sources of potential bias and to ethical issues.

In a typical case-control study, cases and controls are selected from the same source population with two subpopulations: exposed and unexposed to an outcome, e.g. a disease, injury or an accident. The odds ratio of an outcome can be computed based on this design.

The concept of case-control studies

Case-control studies are regarded as the theoretically most appropriate method to calculate risk [3, 4]. By conducting a case-control study the association between a risk factor (e.g. cannabis use) and an outcome measure (e.g. injury resulting from a road accident) can be determined for a defined population. The exposure to cannabis use is measured for both cases and controls. The risk of getting injured is assessed by computing the odds ratio.

If the target population consists of car drivers, an odds ratio of one is assigned to drivers who are not exposed to the independent variable, i.e. who did not use cannabis. If the odds ratio of cannabis-positive drivers is less than one, their risk is lower than the risk of unexposed drivers. If the odds ratio is greater than one, the risk of exposed drivers is higher.

Odds ratio *versus* relative risk

The terms relative risk and odds ratio are often used as if they were synonyms. Technically this is not correct, since relative risk (or risk ratio) compares the probability of injury rather than the odds.

Relative risk is a ratio of the probability of an event occurring in the exposed group *versus* the non-exposed group. It is frequently used in studies with low probabilities, where absolute risk measures will not provide significant differences between exposure and outcome variables. An odds ratio represents the ratio of the odds of an event occurring in one group to the odds of it occurring in another group.

In Table 1, a fictitious example is given of the results of a study on the effects of cannabis use. Cases are injured car drivers, while controls are randomly selected drivers from the same geographical area from which the cases arose. Both groups were tested for the presence of cannabis in blood, resulting in the following table:

Table 1 Example of fictive case-control study.

	Cases	**Controls**	**Total**
Positive	10	20	30
Negative	290	780	1070
Total	300	800	1100

The relative injury risk of cannabis use is:
RR = (positive cases/all positives)/(negative cases/all negatives)
= (10/30)/(290/1070) = 1.23

The odds ratio of being injured after cannabis use is:
OR = (positive cases * negative controls)/(positive controls * negative cases)
= (10 * 780)/(290 * 20) = 1.34

This formula can also be written as:
OR = (positive cases/negative cases)/(positive controls/negative controls)
= (10/290)/(20/780) = 1.34

The relative risk concept is much easier to explain, but relative risk cannot be computed in case-control studies. The impossibility of calculating relative risk in case-control studies is due to the fact that subjects are selected on the basis of outcome, rather than on the basis of exposure. This means that additional information is needed to calculate relative risk, since the probability of the outcome for exposed subjects is unknown. In the example above, the data is not sampled on exposure or disease status, so that it is possible to calculate both relative risk and odds ratios.

The odds ratio can be calculated in case-control studies, and under the rare disease assumption it can be used as an indicator for relative risk [5]. This means that, if an outcome is relatively rare, the odds ratio can be used as an approximation of the relative risk.

Apart from the impossibility of calculating relative risk for case-control studies, a practical advantage of odds ratios is that they are easier to adjust in confounding variables, whereas this is quite difficult for relative risk.

Haworth et al. [6] explained the difference between the odds and the probability of an event as follows: "The odds of an event occurring is equal to the probability of the event occurring divided by the probability of it not occurring. For example, the odds of drawing a diamond from a pack of cards is one-third (one quarter divided by three quarters), compared with the probability which is one quarter".

The concept of relative risk is commonly used in prospective studies such as randomized clinical trials or cohort studies. Odds ratios are favoured for retrospective studies such as case-control studies, where relative risk can not even be calculated.

Matched *versus* population based case-control studies

The literature on the theory of case-control studies [3, 7, 8] suggests that the common method of conducting case-control studies is to select controls to be representative of the population from which the cases arise. Based on Rothman and Greenland [8] the probability of selecting a driver for the control group should be proportional to the amount of time that the driver is driving during the roadside survey. In practice, other exposure indicators are used as well, e.g. traffic volume or trip distribution [6, 9].

If random sampling is not feasible or if it is necessary to eliminate the effects of confounding factors [7] it will be more efficient to match cases and controls. This is also the case if the outcome includes results for different subpopulations [10].

Matching is based on characteristics of the cases which are related to the outcome (confounding variables). The distribution of the confounding factors used for matching should be the same in both the control and the case groups. Common confounding factors that have been found in literature on epidemiological studies to determine the risk of driving under the influence are: age, gender, time of day, day of week, and road type.

Matching all confounding variables is not efficient, however, and almost impossible in practice. Besides, it could lead to overmatching and thus to less precise estimates. Wacholder et al. [11] state that "matching should be considered only for risk factors whose confounding effects need to be controlled for, but that are not of scientific interest as independent risk factors in the study".

Matching for a subset of confounding factors is commonly applied in case-control studies. It implies that controls are selected to match a selection of confounding variables. Several case-control studies that have assessed the relative risk of driving under the influence of alcohol have matched their controls regarding location, direction of traffic, day of week, and time of day. Matching for confounding factors such as age and gender would lead to practical problems and less efficiency. Instead, the adjustment for these confounding factors was performed afterwards in the statistical analysis.

Weaknesses of case-control studies

The main reason for conducting case-control studies is based on the methodological strength of this study type. The case-control design is very suitable when dealing with rare diseases and when many factors for the disease under study need to be evaluated. However, different practical and ethical issues regarding case-control studies have been mentioned in the literature as well. Berghaus et al. [1] mention high cost and difficulties with the design. The results can be biased in many ways: by the selection of cases and controls, by the choice of confounding factors, and by non-response and missing cases.

The non-response rate will increase when the sample collection becomes more invasive. This problem arises particularly when blood samples are required from control subjects [12]. If a study faces a large proportion of refusers, information on gender and age, self-reported drug use and clinical signs of impairment can be useful for determining whether, and to what extent, the non-response group would differ from the response group. These characteristics should therefore be available for both groups.

The need for ethical approval can also lead to difficulties when conducting case-control studies. In Norway, a case-control study suffered difficulties due to requirements of the ethics committee [13] and, in the United Kingdom, a case-control study was cancelled because no approval was given by the ethics committee, and

additional case-samples did not meet the requirements for comparison with the roadside (control) samples [14].

Alternatives for case-control studies are "culpability" or case-crossover studies, pharmaco-epidemiological studies and experimental studies. These alternative study types are, in general, less difficult and expensive to conduct than case-control studies. However, some particular methodological issues are associated with these study types when used for calculating relative risk. [1, 15].

Examples of case-control studies

As mentioned before, only a few case-control studies have been conducted to assess the relative risk of driving under the influence of psychoactive substances other than alcohol.

Haworth et al. [6] conducted a case-control study to estimate the risk of fatal single-vehicle accidents in Victoria, Australia during the year 1995. A total number of 100 control sites were selected in a structured way according to location type (based on the proportion of single vehicle fatal crashes on roads inside and outside a built-up area), road class (based on the amount of travel on the type of road) and time of day (based on amount of travel during day and night and on weekends and weekdays) to match the expected 100 crash sites as much as possible.

At each location two drivers were stopped at random by the police, and were interviewed. Prevalence of cannabis among the control group was based on self-reporting, and prevalence among the cases was based on toxicology reports. Table 2 shows the calculated odds ratios of this study at a 95 % confidence level. The confidence interval is given for each odds ratio. An effect is not significant when the confidence interval includes one.

The unadjusted odds ratio for cannabis was 38.2 (CI 13.8–105.8). Adjustment for both BAC and age group led to a much lower odds ratio of 6.4 (CI 1.5–28.0), mainly because of the relationship between cannabis and BAC. The adjustment for sex or age lowered the odds ratio only slightly. Adjustment for sex, age, and BAC together was not calculated, however. A comparable study in the Netherlands showed particularly higher prevalence of THC in both a hospital and general driv-

Table 2 Unadjusted and adjusted odds ratio's [6].

Psychoactive substance	Unadjusted odds ratio (95 % CI)	Adjustment for age (95 % CI)	Adjustment for sex (95 % CI)	Adjustment for BAC (95 % CI)	Adjustment for BAC (≥ 0.5 g/l) and age (95 % CI)
THC	38.2 (13.8–105.8)	35.1 (12.2–100.8)	35.6 (12.8–99.1)	9.3 (2.3–37.4)	6.4 (1.5–28.0)

ing population for young male drivers [9]. Unfortunately, in the Haworth et al. study the odds ratio was not published for the combination BAC, age, and sex.

Mura et al. [16] conducted a case-control study in France between June 2000 and September 2001 in order to determine the prevalence of psychoactive substances in blood samples of hospitalised car drivers involved in non-fatal accidents and to compare these outcomes with those of patients who attended the same emergency units for non-traumatic reasons.

Cases and controls were matched by sex and age. Blood and urine samples were collected from all subjects; if case urine sampling was not possible, sweat samples were collected.

Table 3 shows the odds ratios of the Mura et al. study at a 95 % confidence level. No additional adjustments for confounding factors were made, except for the initial matching for age and gender. For drivers aged 18–26, odds ratios were calculated for THC and alcohol (BAC > 0.5 g/l). For the odds ratio calculations of morphine and benzodiazepines all age groups were included.

The odds ratio of THC alone was 2.5 (CI 1.5–4.2), for the combination of alcohol and THC 4.6 (CI 2.0–10.7), for morphine 8.2 (CI 2.5–27.3) and for benzodiazepines 1.7 (1.2–2.4). The main flaw of this study is that the choice of the control sample is incorrect from a methodological point of view, since the control sample was not drawn from the same population from which the case sample arose. Thus, one of the fundamental principles of case-control studies was violated [8]. The results are therefore of limited value, indicative at most.

Table 3 Odds ratios [16].

Psychoactive substance	Odds ratio (95 % CI)
THC alone	2.5 (1.5–4.2)
THC + alcohol (BAC > 0.5 g/l)	4.6 (2.0–10.7)
Morphine (> 20 ng/ml)	8.2 (2.5–27.3)
Benzodiazepines	1.7 (1.2–2.4)

Table 4 Unadjusted and adjusted odds ratios [17].

Psychoactive substance	Unadjusted odds ratio (95 % CI)	Adjustment for age, sex, hour and day (95 % CI)
THC	2.0 (1.4–2.9)	1.6 (1.1–2.4)
Cocaine	3.7 (1.1–13.1)	4.5 (1.2–16.3)
Benzodiazepines	3.5 (2.3–5.4)	3.9 (1.5–6.5)

Brault et al. [17] conducted a case-control study in Canada between April 1999 and November 2001. Blood and urine samples of fatally injured drivers were collected, as well as breath, urine and saliva samples of a random sample of drivers which was distributed proportional to the distribution of fatal crashes by time of day and day of week. The control sample was weighted to eliminate over-sampling during the night-time period. An interesting aspect of this study is that it includes both a case-control and a culpability study. A culpability study is a type of case-crossover study where culpability in causing an accident is assessed for a risk factor by comparing the odds of cannabis use by culpable injured drivers and non-culpable injured drivers.

Table 4 presents the adjusted and unadjusted odds ratios at a 95% confidence level. The results of the case-control study were adjusted for age, sex, hour, and day. An odds ratio of 1.6 (CI 1.5–3.4) was calculated for cannabis alone; of 4.5 (CI 1.4–17.4) for cocaine alone, and of 3.9 (CI 1.4–4.3) for benzodiazepines alone. The results of the culpability studies showed lower odds ratios for cannabis and benzodiazepines. Insufficient data were available to calculate the culpability rate of cocaine.

The main weaknesses of this study are the high non-response rate and the use of urine as the body fluid to be analyzed. Since only inactive metabolites of THC can be detected in urine, the relative risk of cannabis use is calculated rather than the relative risk of cannabis impairment [15].

Mathijssen and Houwing [9] conducted a case-control study in the Netherlands, between May 2000 and March 2004, to assess the relative injury risk of psychoactive substance use by car drivers. The study was part of the European Union's IMMORTALproject, which aimed at investigating the influence of chronic and acute impairment factors on driving performance and accident risk. Cases consisted of injured drivers admitted to a regional trauma centre. Controls were selected from the general driving population in the hospital's catchment area. Research locations were distributed along main rural and municipal roads, where almost 90% of all serious injury crashes occurred. Blood or urine samples were taken from both the injured and non-injured drivers.

Before analysis, the case sample was weighted to match the official distribution of seriously injured car drivers by gender in the research region, and the control sample was weighted to match the distribution of traffic flow by time of day and day of week. Odds ratios were calculated by using unconditional logistic regression.

Both adjusted and unadjusted odds ratios are presented in Table 5 at a 95% confidence level. The original IMMORTAL report did not contain adjusted odds ratios. Recent calculations resulted in adjusted odds ratios. After adjustment for year, quarter of the year, day and time-period, gender and age, the following odds ratios were computed at a 95% confidence interval: of cannabis alone 1.29 (CI 0.57–2.95, not significant); of benzodiazepines alone 3.48 (CI 1.29–9.35); of morphine/heroine alone 11.7 (CI 0.63–219, not significant); and of codeine alone 6.89 (CI 1.23–38.6). For amphetamines, ecstasy, cocaine, tricyclic antidepressants and methadone, no odds ratios were calculated due to their absence in the case group.

Table 5 Unadjusted and adjusted odds ratios [9].

Psychoactive substance	Unadjusted odds ratio (95 % CI)	Adjustment for year, quarter of the year, day-and-time, age and sex (95 % CI)
THC alone	1.45 (0.64–3.29) NS	1.29 (0.57–2.95) NS
Morphine/heroin alone	32.4 (1.78–592) NS	11.7 (0.63–219) NS
Codeine alone	3.04 (0.65–14.2) NS	6.89 (1.23–38.6)
Benzodiazepines alone	2.98 (1.31–6.75)	3.48 (1.29–9.35)
Combination of drugs	24 (11.5–49.7)	10.2 (4.38–23.9)
Alcohol (BAC < 0.8 g/l) + drug(s)	12.9 (3.78–44.2)	7.39 (1.99–27.4)
Alcohol (BAC ≥ 0.8 g/l) + drug(s)	179 (49.9–638)	104 (34.2–316)

The collection by two different sample techniques is a methodological weakness and could lead to biased results. Comparison of the positive test results of blood and urine samples with self-reported use and clinical signs of impairment, however, indicated that the biasing effect of uneven distribution of blood and urine samples over the hospital and road samples was probably minimal.

In New Zealand, a case-control study was conducted to assess the relationship between recent cannabis use in the form of marijuana and car crash injury, and between habitual marijuana use and car crash injury [18]. The case group consisted of drivers involved in injury crashes, including fatal crashes. The control group was sampled from drivers in traffic on random roads in the region. Marijuana use was based on self-reporting from an in-depth interview.

Table 6 presents the adjusted and unadjusted odds ratios of recent cannabis use at a 95 % confidence level. Adjusted odds ratios were calculated for three different sets of variables. The first adjustment included age and sex, the second included age, sex, and a set of other confounding factors mentioned in relevant literature, and the third set included the previous variables plus a set of additional risky driving variables such as BAC level and seat-belt use. The authors reported adjusted

Table 6 Unadjusted and adjusted odds ratios [18].

Psycho-active substance	Unadjusted odds ratio (95 % CI)	Adjustment for age and sex (95 % CI)	Adjustment for variable group I [1] (95 % CI)	Adjustment for variable group I plus BAC, seat-belt use and travelling speed (95 % CI)
THC	11.4 (3.6–35.4)	6.0 (1.8–20.3)	3.9 (1.2–12.9)	0.8 (0.2–3.3) NS

[1]age, sex, ethnicity, driving exposure, age of vehicle, time-of-day and number of passengers

odds ratios for these three sets of variables of respectively 6.0 (CI 1.8–20.3); 3.9 (1.2–12.9); and 0.8 (CI 0.2–3.3 not significant).

The use of interviews instead of samples of body fluids is a major weakness of this study design. Furthermore, the choice of confounding factors is questionable, since some of the variables, such as sleepiness, may be associated with marijuana use. The authors have acknowledged this problem but indicated that it is difficult to estimate the size and direction of this potential bias. Finally, non-response among controls was 21.2%, which is quite a large proportion, especially since only 0.5% of the remaining drivers in the control group reported recent marijuana use. In comparison, 7.2% of the accident-involved drivers refused to cooperate and 5.6% reported recent marijuana use. Although this non-response group is much smaller, it still exceeds the proportion of marijuana-using drivers, thus affecting the validity of the study.

Comparability of case-control studies

As stated earlier, the number of case-control studies that have been conducted to assess the risk of driving under the influence of psychoactive substances other than alcohol is very low. But even a limited number of studies can provide good estimates of the risk of drug driving. This is only the case, however, when the selected studies all have a good methodological foundation and when study outcomes are comparable.

The comparability of the results of case-control studies depends on several indicators. Some indicators can be regarded of higher importance than others, however. To evaluate comparability, the following indicators can be used:

- substances
- type of cases
- type of controls
- transport mode
- sample of body fluid from cases
- sample of body fluid from controls
- response rate among cases
- response rate among controls
- confidence level
- lower limit of substance concentration
- confounding factors

Table 7 provides an overview of main indicators for the five recently conducted case-control studies. In this table only the results for THC have been used, since this was the only drug type that was analyzed in all five studies.

The designs of four of these studies are quite comparable for the type of cases and controls. Only Mura et al. [16], however, did not use randomly selected drivers as controls, but instead non-crash-involved patients in possession of a driving license.

Table 7 Comparability indicators case-control studies.

	Indicator									
	Cases	**Controls**	**Vehicle type**	**Sample matrix cases**	**Sample matrix controls**	**Response rate cases**	**Response rate controls**	**Confidence level**	**Lower limit substance conc.**	**Confounding variables**
Haworth et al. (1997)	Drivers of fatal single vehicle crashes	Stratified sample of non-crash involved car drivers	Cars and light commercial vehicles (6% of the cases and 9% of the controls)	Toxicology reports coded cannabis metabolite was found in blood or urine	Interview marijuana use within 12 hours prior to recruitment	82%	95%	95%	Unknown	BAC and age
Mura et al. (2003)	Injured car drivers aged 18–26, excluding fatally injured drivers	Non-traffic accident involved patients in possession of a driving license matched by sex and age	All cars	Blood	Blood	96%	96%	95%	THC 1 ng/ml	Sex and age by matching
Brault et al. (2004)	Fatally injured drivers of passenger vehicles	Stratified sample of non-crash involved car drivers	All passenger vehicles	Urine sample	Urine sample	63%	49.6%	95%	25 ng/ml THC-COOH	Age, sex, hour, and day

Table 7 (*continued*) Comparability indicators case-control studies.

	Indicator									
	Cases	**Controls**	**Vehicle type**	**Sample matrix cases**	**Sample matrix controls**	**Response rate cases**	**Response rate controls**	**Confidence level**	**Lower limit substance conc.**	**Confounding variables**
Mathijssen and Houwing (2005)	Seriously injured car drivers	Stratified sample of non-crash involved car drivers	All passenger cars except commercial vehicles	Blood or urine sampling	Urine or blood sampling	89%	89%	95%	5 ng/ml THC in blood and 50 ng/ml THC-COOH in urine	Age, sex, year, quarter of the year, day, and-time
Blows et al. (2004)	Car drivers involved in serious injury crashes	Stratified sample of non-crash involved car drivers	All cars	Interview acute marijuana use within 3 hours prior to crash	Interview acute marijuana use within 3 hours prior to recruitment	92.8%	78.8%	95%	-	Age, sex, ethnicity, driving exposure, vehicle age, time of day, BAC, seatbelt use and speed

The four remaining studies all vary in the way they collected data on cases and controls. Blows et al. [18] used interviews for both cases and controls, Haworth et al. [6] used toxicological reports for cases based on blood and urine samples and interviews for the subjects in the control group, Mathijssen and Houwing [9] used blood or urine for the cases and urine or blood for the controls, whereas Brault et al. [17] used urine for both cases and controls. In order to estimate the relative risk of driving under the influence of psychoactive substances, urine is less useful than saliva and blood, since the detection window is much larger, which has definite consequences for its validity as a body fluid sample.

Furthermore, the response rate of the different studies varies between 63 % and 96 % for the cases group and between 49.6 % and 96 % for the controls. This is mainly a validity issue: the higher the refusal rate, the higher the risk of bias. Therefore, it is recommended that characteristics of both refusing and participating subjects be examined in order to determine whether the validity of the study is affected.

Adjustment for confounding factors also differs from study to study. The impact of confounding factors on the odds ratio can be substantial. Haworth et al. [6] found an unadjusted odds ratio for cannabis of 38.2, adjusting for age and gender resulting in lower odds ratios of respectively 35.1 and 35.6. Adjustment for alcohol use resulted in a much lower odds ratio of 9.3, and adjustment for both alcohol and age even in an odds ratio of 6.4.

Most studies included at least age, gender, and time of day as confounding variables or matched for these variables when selecting controls. Blows et al. [18] included many more possible confounding factors in the analysis, which probably resulted in overmatching. Beyond that, not all factors that were used in this study can be regarded as confounding factors.

For reasons of validity and comparability, it is recommended that adjustments be made for a minimum set of confounding factors, including at least gender, age, day of the week, and time of the day. These confounding factors can be corrected for by matching or by adjusting during the statistical analysis

Finally, the cut-off levels of the analyzed body fluids differ. A higher cut-off level will result in a smaller proportion of positive subjects. In the case of these five selected studies, the differences between the cut-off levels were small and will probably hardly affect the comparability.

Discussion

Case-control studies have their strengths, but also their weaknesses. The methodology is hard to implement and there are many sources of potential bias that could affect the validity of the study results. On top of that, ethical issues may arise, especially in collecting samples of body fluids among controls. Case-control studies are therefore not commonly used as a method to assess the risk of driving under the influence of psychoactive substances other than alcohol.

Another problem is lack of comparability between the case-control studies that have been conducted. The adjusted odds ratios of cannabis use in the selected studies vary from 6.4 to 0.8 (NS). It is likely that this variation is at least partly caused by differences in research design, causing incomparable results even when the odds ratios seem to be more or less the same.

Due to the limited number of case-control studies and the insufficient comparability of the study results, no commonly accepted risk estimations for drugs are yet available.

In 2006 a consensus meeting was organised by the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) to develop standards for future research. These recommendations for standardized research include legal/ethical issues, subject and study design issues, and core data parameters. At this meeting cut-off levels were recommended for blood, saliva and urine. These cut-off levels are applied in the European DRUID project in which seven additional case-control studies are being conducted. To ensure comparable outcomes, more detailed guidelines have been prepared for the design of case-control and prevalence studies [19].

In spite of the guidelines, the design of the DRUID case-control studies still varies substantially due to practical and ethical limitations within the participating countries. In order to make the results of the various studies comparable with each other and with previous studies, a special study will aim at gaining insight into the effects of these differences and into the possibilities to apply transformation rules.

An important source of potential bias is the choice of different body fluids to be collected among cases and controls. As mentioned before, for comparisons between cases and controls blood is the best body fluid. A great disadvantage of taking blood samples from randomly selected drivers is the invasiveness of the method, which could lead to high non-response rates that undermine the validity of the study.

An alternative to blood sampling at the roadside is saliva sampling, since saliva can also be used to detect recent drug use. But there is no fixed relationship between psychoactive substance concentrations in blood and saliva [20]. Comparing results from blood testing among cases and saliva testing among controls may therefore seriously bias the study results.

Finally, the question remains as to whether high non-response rates, with the increased risk of selection bias, outweigh the bias resulting from the use of different body fluids among cases and controls. The calculation of dose-related odds ratios will be very problematic when different body fluids are analyzed for cases and controls.

Summing up, although strict case-control studies are preferable in many cases from a methodological point of view, the problems and pitfalls are numerous. Considerable effort and financial investment are necessary to get round the many difficulties.

The comparability, and thus the usability, of future case-control studies can be improved by standardizing the study design. Furthermore, guidelines and recommendations are needed to provide solutions for practical, ethical, and legal issues regarding case-control studies.

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Prescribing and dispensing guidelines for medicinal drugs affecting driving performance

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Abstract

This chapter aims to provide practice-oriented information for prescribing physicians and dispensing pharmacists who want to provide their patients with adequate advice based on a clear understanding of the risks of accident involvement under different treatment conditions. Specific attention will be given to the application of a graded-level warning system based on categorization systems for psychotropic medicines that have been introduced,, and sometimes legally implemented, in several European countries. This warning system allows physicians and pharmacists to select the least impairing medicines within a therapeutic class. Advice for the patient based on three categories has been described in clear instructions, allowing the patient to make the right decision.

For the most frequently used drug classes (antihistamines, antidepressants, hypnotics and tranquillizers) information will be provided on drugs with little or no impairment within the respective classes, and risk factors (e.g. liver and./or renal dysfunction, drug–drug interactions) that might increase impairing effects. If drugs with little or no impairment can not be prescribed, specific patient information will focus on recognizing signs of impaired performance.

Introduction

Driving a motor vehicle is a complex task that requires the possession of sufficient cognitive, visual and motor skills. The assessment of whether a patient is medically fit to drive can be addressed to physicians under various conditions. First of all, whether neurological disorders (stroke, traumatic brain injury, peripheral neuropathy, dementia, Parkinson's disease and epilepsy) compromise the functions and skills required for safe driving must be considered. In those circumstances physicians have to be formally trained in this area to assess medical fitness to drive. Secondly, physicians can prescribe medications that provide patients with a significant adverse effect across a range of skills required for safe driving. In most situations patients will obtain medications dispensed by pharmacists who, similar to physicians, have a responsibility to provide the patient with information as to how to use the medication safely. Practical recommendations to prescribing physicians and dispensing pharmacists are hardly known, and practitioners admit that there is a need to use guidelines for safe prescribing and dispensing of medicinal drugs to those patients who operate motor vehicles, or other transportation vehicles.

In our developed society, driving a motor vehicle is a central activity in our daily lives and considered to be essential for an independent life-style and personal autonomy. It provides access to employment, whereas mobility and quality of life are determining elements in patients' perspectives of an active social role. The question of driver fitness under psychotropic medications has become extremely important and prerequisites and restrictions to driving are essential elements of each consultation with a patient who drives a motor vehicle. The use of medication with the least impairing properties is considered to be a patient right, not only from a driver's perspective but also from a medication safety perspective.

Medicine has developed over the last decades and many new medicinal drugs appear on the market, with the intention of replacing older ones where adverse reactions might affect a range of psychomotor functions. Most well-known examples are the introduction of SSRIs (Selective Serotonin Reuptake Inhibitors); the noradrenergic and specific serotonergic antidepressants (NaSSA) are replacing the tricyclic antidepressants (TCAs). Non-sedating antihistamines have replaced the older, sedating medications for the treatment of allergic conditions, and newer hypnotics such as zaleplon, zolpidem and zopiclone replace older benzodiazepines, although beliefs about safety are not supported by research findings in all cases.

This chapter aims to discuss the present state-of-the-art with respect to practical guidelines with emphasis on prescribing and dispensing practices. The authors provide several recommendations as to how to improve the application of existing knowledge by using a graded level-warning system, such as that recently implemented in France. The prescribing and dispensing guidelines allowing physicians and pharmacists to prescribe and dispense the least impairing medicinal drugs for drivers are presented based on a report by a working group within the International Council on Alcohol, Drugs and Traffic Safety (ICADTS). Special attention has been given to include prescribing and dispensing information that will allow patients to be more aware of recognizing the signs of impaired driving performance if drugs with little or no impairment cannot be used to treat their disorders.

Application of information

In practice, physicians and pharmacists update their knowledge on the behavioural toxicity of medical drugs from three major sources:

- Package inserts approved by the drug regulatory authorities provide some information about known impairment of driving ability caused by the relevant substances;
- Articles in scientific journals and drug bulletins which discuss impairment of psychomotor performance in healthy subjects and/or patients under various test conditions attributed to various substances or groups of substances;
- Product-specific mailings by the pharmaceutical industry claiming that their products are safe for drivers, or giving general warnings.

Physicians and pharmacists deal with individuals. They have to decide whether or not a particular patient will become an unsafe driver after using a specific psychotropic medication. Population studies are not easy to interpolate for the individual. When clear statements are made about driving risk, the prescriber and dispenser may not know the scientific basis for this advice, and therefore cannot judge its validity for their patients.

Consequently, many physicians find that the problem of drugs and driving remains a complex one, and that no solution is evident. Clinicians know that medication can produce unpredictable effects on performance. Clinical experience teaches that drug side-effects vary from person to person and are compounded by polypharmacy and self-medication. Impairment is often worse when drugs are taken in combination with alcohol. The picture is further complicated by recognizing that some medical conditions may themselves impair driving, if not treated properly with medication (e.g. epilepsy, allergic rhinitis, depression). The general principle is that it is usually best clinical practice to prescribe the least impairing member of a therapeutic class, where a suitable drug is available.

When physicians have doubts about the ability of a patient to drive safely when undergoing drug treatment, they need to advise the patient to avoid driving. The required counseling is time-consuming. The message that medication is necessary but makes driving hazardous is hard for the prescriber to give and for the patient to hear. Proper explanation requires a clear understanding of the risks of accident involvement under different treatment conditions.

There are good examples of pharmacoepidemiology research, in which drug-use data in a given population is linked to accident data in the same population to estimate relative risk. These studies show that patients exposed to various types of psychotropic medication are at increased risk, particularly due to benzodiazepines and one cyclopyrollone hypnotic zopiclone used in therapeutic doses [1–4]. Table 1 presents relative risks of injurious road traffic accidents associated with the use of particular hypnotic and anxiolytic drugs and comparable blood alcohol concentrations from the Grand Rapids Study [5].

The risk is highest during the first two weeks of treatment. Extremely high relative risks have been reported with certain benzodiazepines: for example, a 5-to 6-fold increase in accident risk, which is comparable to a blood alcohol concentration of

Table 1 Relative risks of injurious road traffic accidents associated with the use of particular hypnotic and anxiolytic drugs and comparable blood alcohol concentrations.

Drug	Relative Risk	Comparable to BAC (%)	Reference
Diazepam	3.1	0.075	[3]
Flurazepam	5.1	0.095	[3]
Lorazepam	2.4	0.070	[3]
Oxazepam	1.0	0.050	[3]
Triazolam	3.2	0.075	[3]
Zopiclone	4.0	0.080	[4]

0.1% [6]. This implies that patients who commence treatment with a benzodiazepine must be advised that they should not drive in the first two weeks of treatment. If physicians do not give this advice, their patients have an increased risk of being involved in accidents, but do not know that they are taking the risk. Patients have a right to receive adequate information to enable them to decide whether or not to drive.

A graded level warning system

A proposal to introduce a graded level warning system for medicinal drugs affecting driving performance was presented to the European Union in 1991. Such a system would allow prescribers to choose the least impairing medication within each therapeutic class of drugs [7]. The European Union (EU) has formally defined criteria that allow categorization of drugs according to their impairing properties. The EU's Committee for Proprietary Medicinal Products (CPMP) Operational Working Party stipulated, in its Note for Guidance for the Summary of Product Characteristics (III/9163/90-EN, Final approval 16 October, 1991), that all medicines registered after 1 January 1992 can be categorized within the "Warning" section of package inserts with respect to "Effects on ability to drive or operate machines". Article 4.7 in the original Note for Guidance states the following:

On the basis of the pharmacodynamic profile, reported ADR's (adverse drug reactions) and/or impairment of drug performance or performance related to driving, the medicine is:

a) presumed to be safe or unlikely to produce an effect;
b) likely to produce minor or moderate adverse effects;
c) likely to produce severe effects or presumed to be potentially dangerous.

For situations b) and c), special precautions for use/warnings relevant to the categorization should be mentioned.

Although a framework has been proposed, no pan-European body is categorizing drugs on the basis of their hazard potential for driving [8, 9]. Belgium was the first country to introduce a categorization system for 180 medicinal drugs addressing health care professionals and patients [10], followed by Spain [11] and France [12]. Slovenia introduced the categorization system in 2007 [13] and in the Netherlands a categorization system has been introduced in October 2008 [14]. It is to be noticed, in the case of France, that the categorization was not a purely scientific proposal, but legally binding as published in the Official Journal of the French Republic. These categorization systems were not fully equivalent in either the number of categories or in the substances included.

Labeling regarding medicinal drugs and driving as a dichotomous system has been in existence for many years in the Netherlands (the yellow/black label) and most Nordic countries (the red triangle), except in Sweden, where the red triangle was removed from the medicines in 2007, but the situation was clearly improved in France. In fact, the labeling of medicinal drugs became widespread in France when the red triangle with a black car inside was first introduced. With the new regulation in France, three categories are used, which are also reflected by three warning symbols that are printed on the medicine-box. The French descriptions consider the perspective of the patient, allowing him or her to act and to decide on the best way to respond to the warning given for a specific category. It focuses more on the

Warning symbol	Description of category
	Background color warning symbol: yellow Be careful. Do not drive without having read the leaflet. **Soyez prudent** Ne pas conduire sans avoir lu la notice
	Background color warning symbol: orange Be very careful. Do not drive without advice of a medical professional. **Soyez très prudent** Ne pas conduire sans l'avis d'un professionnel de santé
	Background color warning symbol: red Attention: danger. Do not drive. **Attention, danger: ne pas conduire** Pour la reprise de la conduite, demandez l'avis d'un médecin

Figure 1 Warning labels and categories in France (2005).

practical use of the various categories, which is an advantage. It also takes into account the judgement of the physician (Fig. 1).

New legislation concerning driver-impairing medicines has recently been approved in Spain [15]. It includes the introduction of a warning label on medicines that can impair driving. The label consists of a black car inside a red triangle, which is very similar to the first French warning label. At this moment no list of substances exists with the label.

Categorization system for medicinal drugs affecting driving performance

After the publication of the report of the ICADTS Working Group on Prescribing and Dispensing Guidelines for Medicinal Drugs affecting Driving Performance in 2001 (available at: www.icadts.org), the need for a list with medicinal drugs categorized according to their impairing properties came under discussion. The practical use of the guidelines would benefit from the availability of such a list, because it would allow the prescribing doctor and dispensing pharmacist to look for safer alternatives within one specific therapeutic class.

The experts from the ICADTS working group decided to use a calibration scheme in which the impairment description for medicinal drugs is compared with blood alcohol concentrations, as presented in Table 2.

Data collected in experimental research, in which on-the-road driving tests have been applied with most frequently used medicinal drugs and alcohol (as "calibration"), have allowed researchers to interpret weaving effects by any drug as equivalent to that produced by a particular blood alcohol concentration. It will be easier to understand the severity of impairment by medicinal drugs if this concept could be communicated. This calibration scheme was proposed as part of the clarifica-

Table 2 Description of impairment within the categories compared with impairment based on blood alcohol concentrations.

Category	Impairment description for medicinal drugs	Comparison with Blood Alcohol Concentration (BAC)
I	Presumed to be safe or unlikely to produce an effect	Equivalent to BAC < 0.2 g/l (< 0.02 %)
II	Likely to produce minor or moderate adverse effects	Equivalent to BAC 0.2–0.5 g/l (0.02–0.05 %)
III	Likely to produce severe or presumed to be potentially dangerous	Equivalent to BAC > 0.5 g/l (> 0.05 %)

tion of the terminology of the three categories, because this was considered to be more meaningful, since 0.5 g/l (0.05 %) is the legal limit in the vast majority of EU member states.

Although differences in descriptions exist, it is possible to agree on the categorizations based on existing systems in the various countries, and therefore the ICADTS Working Group has proposed the following descriptions for interpretation and practical use of its list (Table 3).

Table 3 Interpretation and practical use of impairment descriptions for each category.

Description of category	Interpretation and practical use
Category I: **Presumed to be safe or unlikely to produce an effect**	In various experimental circumstances negligible or no impairment of driving performance or performance related to driving is repeatedly demonstrated. Also for medicinal drugs that are presumed not to be dangerous based on their pharmacological profile, even though there are no experimental studies that support this presumption. For the most frequently used drugs in this category the effect has been assessed in over-the-road driving tests as equivalent to blood alcohol concentrations < 0.5 g/l (< 0.05 %). *Advice for the patient:* Be careful not to drive before having read the warnings in the package insert.
Category II: **Likely to produce minor or moderate adverse effects**	Some impairment of driving performance or performance related to driving is seen in various experimental laboratory circumstances. Also for drugs that will not produce severely adverse effects, but because of a lack of sufficient experimental studies it can not be established if the effect is moderate, light or absent. For the most frequently used drugs in this category the effect has been assessed in over-the-road driving tests as equivalent to blood alcohol concentrations 0.5–0.8 g/l (0.05–0.08 %). *Advice for the patient:* Do not drive without consulting a healthcare professional about the possible impairing effects.
Category III: **Likely to produce severe effects or presumed to be potentially dangerous**	In various experimental circumstances gross impairment of driving performance, or performance related to driving, is repeatedly seen. Also for drugs presumed to be potentially dangerous based upon their pharmacological profile, but there are not sufficient experimental studies to support this presumption. For the most frequently used drugs in this category the effect has been assessed in over-the-road driving tests as equivalent to blood alcohol concentrations > 0.8 g/l (> 0.08 %). *Advice for the patient:* Do not drive when this drug is taken and consult a healthcare professional as to when to start driving again after evaluation of the treatment outcomes.

Limitations of the ICADTS list

The ICADTS categorization list [see Appendix and http://www.icadts.nl/reports/medicinaldrugs2.pdf] is based on the Belgian, Spanish and French categorization lists, and proposes three categories. It was not the objective of the ICADTS Working Group to review all available literature again in assigning categories for medicinal drugs, and thereby duplicating the work that has been done in Belgium, Spain and France, respectively in 1999, 2002 and 2005.

An updated review will be done in the near future within the Sixth Framework Programme of the European Union as an Integrated Project entitled DRUID (Driving under the Influence of Drugs, Alcohol and Medicines) aimed to be concluded in October 2010. Within DRUID, a review of existing classification efforts has been published as Deliverable 4.1.1 (available at: www.druid-project.eu).

Furthermore, the list will only contain medicinal drugs which are on the market in either Belgium, Spain or France and therefore will not cover all drugs within a therapeutic class.

Another limitation is the lack of information in the categories on the various dosages that are used for different medicinal drugs. As a general rule the categories are assigned to the drug at the normal therapeutic dosage given to an adult for the main indication of the drug. If higher dosages are taken one should consider the drug to be categorized as one category higher if not yet assigned to the highest category.

Guidelines for prescribing and dispensing medicinal drugs affecting driving performance

Although it is the objective of the ICADTS list to support the physician and pharmacists in selecting the safest alternatives within each therapeutic class, if available, specific attention should be given to general prescribing and dispensing guidelines (Table 4).

For some frequently used drug classes, more specific information can be provided to guide the physician and pharmacist in prescribing and dispensing these psychotropic medicines (Tables 5a and 5b).

Table 4 General guidelines for prescribing and dispensing medicines with impairing potential.

Prescribing Guidelines	Dispensing Guidelines
1. Realize that the use of some psychoactive drugs has been associated with an increased risk of causing an injurious accident and that patients should receive this information.	1. Discuss with prescribing physicians what patient information (written and oral) should be provided at the first delivery of a particular impairing drug
2. Consider an alternative in the light of experimental research showing large differences between the effects on driving performance of various drugs within the same therapeutic class.	2. Inform the prescribing physician that alternative drugs exist in case a drug in class II or III has been prescribed, and inform the patient.
3. Start with the lowest doses of psychoactive medical drugs and whenever possible avoid multiple dosing over the day.	3. Advise the physician to prescribe the lowest effective dose of a particular psychoactive medicinal drug and to avoid multiple dosing over the day. Inform the patient.
4. Do not reflexively "double the dose" if patients fail to respond to psychoactive medication.	4. Advise the physician to try another drug if the patient reports a lack of efficacy after beginning of treatment and inform the patient. If higher doses are needed advise the patient to use the largest part before sleep (if compatible with the therapeutic regimen).
5. Avoid prescribing different psychoactive drugs in combination.	5. Explain to the patient that poly-therapy with psychoactive drugs is always an experiment with the patient's safety and avoid driving if treatment cannot be adjusted.
6. Do not rely solely upon manufacturers' advice for counselling patients about the effects of drug upon driving.	6. Explain to the patient why warnings provided by the manufacturer about their drug's effects on driving are vague, illogical and sometimes misleading.
7. Advise patients concerning the ways they can minimize the risk of causing a traffic accident if it is impossible to avoid prescribing an obviously impairing drug or one with unknown impairing potential (see next Table).	7. Advise the patient on ways they can minimize the risk of causing a traffic accident if they have to use a drug with an impairing potential (see next Table).
8. Monitor the patient's driving experience with the drug.	8. Monitor the patient's driving experience with the drug (e.g. at the first refill) and report back to the physician or ask the patient to inform the physician.

Table 5a Specific guidelines for prescribing and dispensing antihistamines and antidepressants with impairing potential.

Drug class	Drugs with little or no impairment	Risk factors	Prescribing information	Dispensing Information
Anti-histamines	Ebastine 20 mg OD Fexofenadine 60 mg b.d.s. or 120 mg/180 mg OD Loratidine 10 mg OD	Liver and/or renal dysfunction		1. Avoid alcohol while taking this drug If drugs with little or no impairment can NOT be prescribed and/or at the beginning of treatment (also with least impairing one) focus on: 2. Recognize signs of impaired driving performance (stop for rest if any occur): • Blurred vision • Difficulty in concentrating or staying awake • Unusual surprise by ordinary traffic events • Not being able to remember how exactly you came at destination • Difficulty in holding steady course in traffic lane
Anti-depressants	Fluoxetine 20 mg OD Moclobemide 200 mg b.d.s. Paroxetine 20 mg OD	No specific risk factors known	Avoid combined use of fluoxetine and nonselective MAOIs, tryptophan, selegiline, terfenadine (adverse drug interactions)	1. Avoid alcohol while taking this drug.

Note: The sequence in which the safer alternatives are mentioned is based on alphabetical order and does not express any therapeutic preference (for references please see http://www.icadts.nl/reports/medicinaldrugs1.pdf).

Table 5a (*continued*) Specific guidelines for prescribing and dispensing antihistamines and antidepressants with impairing potential.

Drug class	Drugs with little or no impairment	Risk factors	Prescribing information	Dispensing Information
			Avoid combined use of moclobemide and dextromethorphan, (tricyclic) antidepressants, (pseudo)ephedrine (adverse drug interactions) Avoid combined use of paroxetine and nonselective MAOIs, and selegiline (adverse drug interactions)	If drugs with little or no impairment can NOT be prescribed and/or at the beginning of treatment (also with least impairing one) focus on: 2. Recognize signs of impaired driving performance (stop for rest if any occur): • Blurred vision • Difficulty in concentrating or staying awake • Unusual surprise by ordinary traffic events • Not being able to remember how exactly you came at destination • Difficulty in holding steady course in traffic lane
	Venlafaxine 75–150 mg q.d. (an SNRI effective in more than 80% of patients with generalized anxiety disorders)	No specific risk factors known	Avoid combined use of venlafaxine and nonselective MAOIs (adverse drug interactions)	

Note: The sequence in which the safer alternatives are mentioned is based on alphabetical order and does not express any therapeutic preference (for references please see http://www.icadts.nl/reports/medicinaldrugs1.pdf).

Table 5b Specific guidelines for prescribing and dispensing hypnotics and tranquillizers with impairing potential.

Drug class	Drugs with little or no impairment	Risk factors	Prescribing information	Dispensing Information
Hypnotics	> 10 h post dosing; taken at night: Lormetazepam 1 mg Temazepam 10 mg Zolpidem 10 mg	Combination with other psychoactive drugs Liver and/or renal dysfunction (elderly patients: half the normal dose)	Avoid prescribing for longer than 2-weeks	1. Avoid alcohol while taking this drug if drugs with little or no impairment can NOT be prescribed and/or at the beginning of treatment (also with least impairing one) focus on: 2. Recognize signs of impaired driving performance (stop for rest if any occur): • Blurred vision • Difficulty in concentrating or staying awake • Unusual surprise by ordinary traffic events • Not being able to remember how exactly you came to destination • Difficulty in holding steady course in traffic lane 3. Avoid taking longer than 2–4 weeks and more than one at night

Note: The sequence in which the safer alternatives are mentioned is based on alphabetical order and does not express any therapeutic preference (for references please see http://www.icadts.nl/reports/medicinaldrugs1.pdf)

Table 5b (*continued*) Specific guidelines for prescribing and dispensing hypnotics and tranquillizers with impairing potential.

Drug class	Drugs with little or no impairment	Risk factors	Prescribing information	Dispensing Information
Tranquillizers	Buspirone 10 mg b.d.s.	No specific risk factors known	Avoid combination with selective serotonin reuptake inhibitors (SSRIs) because of reduced therapeutic effect Consider combination for 1 week with oxazepam 10 mg t.d.s. if therapeutic response seems to be inadequate (forbid driving during the first week)	1. Avoid alcohol while taking this drug if drugs with little or no impairment can NOT be prescribed and/or at the beginning of treatment (also with least impairing one) focus on: 2. Recognize signs of impaired driving performance (stop for rest if any occur): • Blurred vision • Difficulty in concentrating or staying awake • Unusual surprise by ordinary traffic events • Not being able to remember how exactly you came to destination • Difficulty in holding steady course in traffic lane
	SSRI's are effective in more than 60 % of patients with generalized anxiety disorders : Fluoxetine 20 mg OD Paroxetine 20 mg OD	No specific risk factors known	Avoid combined use of fluoxetine and nonselective MAOIs, tryptophan, selegiline, terfenadine (adverse drug interactions) Avoid combined use of paroxetine and nonselective MAOIs, and selegiline (adverse drug interactions)	
	Venlafaxine 75–150 mg q.d. (an SNRI effective in more than 80 % of patients with generalized anxiety disorders)	No specific risk factors known	Avoid combined use of venlafaxine and nonselective MAOIs (adverse drug interactions)	

Note: The sequence in which the safer alternatives are mentioned is based on alphabetical order and does not express any therapeutic preference (for references please see http://www.icadts.nl/reports/medicinaldrugs1.pdf)

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The relationship between drug use and traffic accident severity

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Abstract

The use of alcohol and certain illicit and psychoactive medicinal drugs has been associated with impaired driving and increased accident risk. Data with respect to the relationship between drug use and the severity of the accident, independent of the increased accident risk, are limited. The objective of this chapter is to evaluate and discuss the available epidemiological studies on the relationship between drug use by drivers and the severity of the accident. Data sources used for the literature search were EMBASE, PubMed and Forensic Science Abstracts 3/0 (FORS®). All databases were searched for references included in the database on January 1, 2008. Search strategy included the different groups of psychoactive substances of interest and traffic accidents in combination with accident severity or injury severity. The number of included publications was 20; they were published between 1983 and 2005. The study population varied from all crash-involved drivers (injured and not injured) to patients admitted to a trauma center (including crash-involved drivers) to fatally crash-involved drivers. The most frequently applied design is the cross-sectional study. In general, exposure assessment was performed by using toxicological results but, in a few studies, prescription data, police officers' observations or questionnaires were used. The effects reported are controversial, i.e. the influence of psychoactive drugs other than alcohol on injury and/or accident severity is not clear. Some discrepancies may be explained by differences in methodological factors, e.g. study population, injury or accident severity measures, and exposure measures.

Introduction

The use of alcohol and certain illicit and medicinal drugs has been associated with impaired driving and increased accident risk [1–4]. The relationship between alcohol/drug use and the severity of the accident (i.e. independent of the increased accident risk) has been studied less. A few studies have been published on the relationship between alcohol use and accident or injury severity [5–8]. Data with respect to the question of whether illicit or medicinal drug use also leads to more severe accidents are even more limited. In relation to road safety, it is not only important to prevent accidents but also to gain insight into factors governing morbidity and mortality. Epidemiological studies try to illuminate associations between exposure and event. The outcome of epidemiological studies may be influenced by several methodological factors such as study design, study population, exposure measurement and possible confounders [9, 10]. However, many practical and ethical reasons hamper the optimal design of epidemiological studies on the relation between drug use in daily traffic and (severity of) accidents. The objective of this chapter is to evaluate and discuss the available epidemiological studies on the relationship between drug use and the severity of the accident in drivers involved in an accident. Although the focus will be on illicit and psychoactive medicinal drugs (e.g. opiates, amphetamines and amphetamine-like substances, cocaine, methadone, cannabinoids, benzodiazepines, barbiturates and tricyclic antidepressants), the relationship between alcohol use and accident severity will be indirectly discussed.

Methods

Data sources

Data sources used for the literature search were EMBASE [11], PubMed [12] and Forensic Science Abstracts 3/0 (FORS®) [13]. EMBASE provides biomedical and pharmacological literature. More than 11 million EMBASE records from 1974 to present and more than seven million MEDLINE records from 1966 to present are available [11]. PubMed is a service of the U.S. National Library of Medicine and includes over 17 million citations from MEDLINE and other life science journals on biomedical articles from the 1950s to present [12]. FORS® database is a product of Forensic Science Service Ltd., and includes more than 70 000 records on, e.g., drugs and toxicology, forensic biology, forensic chemistry, forensic medicine and pathology, from 1976 to present with some earlier material included where relevant [13]. All databases were searched for references included in the database on January 1, 2008. Limits were “English” and “Humans”. Search strategy included the different groups of psychoactive substances of interest (i.e. drugs, opiates, amphetamines, cocaine, methadone, cannabinoids, benzodiazepines, barbiturates, tricyclic antidepressants) and traffic accident in combination with accident severity or injury severity.

Selection

To be included in this overview, the study population had to include crash-involved motor vehicle drivers. The outcome of interest was the relationship between drug use and accident severity, often expressed as injury severity. Studies among trauma patients in general were included when a large number of the patients involved were victims of a road traffic accident. Studies reporting on drug use as a factor in the severity of a specific type of injury, e.g., traumatic brain injury or pelvic trauma, were excluded, even if motor vehicle victims were part of the study population. Review articles, letters without original research data, papers presenting data already published, and case reports were excluded. References from every remaining article were examined and included if relevant to the aim of our overview. Although the relationship between drug use and accident or injury severity was not always the primary aim of the study, an effort was made to include all studies reporting on this relationship. The number of included publications was 20.

Data extraction

Data extracted from each study were first author, year of publication, country, study design, study population, study period, outcome variable with respect to injury or accident severity, substances of interest and method of exposure assessment. When associations between drug use and injury or accident severity were expressed as relative risk (RR) or odds ratio (OR), results were documented, including 95% confidence intervals (CI).

Results

Characteristics of the studies included

Table 1 shows the characteristics of the studies reporting on the relationship between drug use and injury severity [1, 14–30] and/or accident severity [16, 18, 31, 32].

The studies included were published between 1983 and 2005. The study population varied from all crash-involved drivers (injured and not injured), patients admitted to a trauma center (including crash-involved drivers) to fatally crash-involved drivers. The study design most frequently used was the cross-sectional design in which, e.g., severely injured drivers were compared with less severely injured drivers. Exposure assessment was performed by using toxicological results [14, 15, 17–26, 28, 31], prescription data [1, 27] or police officers' observations or statements [18, 30]. The substances of interest other than ethanol varied from benzodiazepines only [14, 20, 21], a limited number of drug classes, to drugs in general, i.e. not specified [16, 18]. Assessment of injury severity was performed by using different trauma scoring systems (e.g. Abbreviated Injury Scale (AIS), Maximum

Table 1 Characteristics of the studies (n total = 20).

Characteristics	Studies n (%)
Study population	
injured and non injured drivers	7 (35)
traffic accident victims admitted to a trauma center	7 (35)
patients admitted to a trauma center, including traffic accident victims	4 (20)
other crash involved traffic accident victims	2 (10)
Study design	
case-control	7 (35)
within person case-crossover	2 (10)
crosssectional	9 (45)
case-series	2 (10)
Study period	
≤ 1990	6 (30)
1991–2000	12** (60)
> 2000	2 (10)
Site	
Europe	10 (50)
USA	9 (45)
Canada	1 (5)
Drug exposure assessment	
toxicological results	13 (65)
prescription data	2 (10)
other or not specified	5 (25)
Outcome of interest*	
injury severity	18 (90)
accident severity	4 (20)
Injury severity or accident severity assessment*	
trauma scoring system	9 (45)
hospitalization yes/no	3 (15)
categorization into groups	10 (50)
other	3 (15)

* categories are not mutually exclusive, ** one study: 1988 to 2000

Abbreviated Injury Severity (MAIS), Injury Severity Score (ISS)) [15, 17, 19, 22–26, 28, 29], hospitalization time [15, 25] and/or by categorization into groups [1, 14, 16, 18, 20, 21, 26, 27, 29], e.g., single, multiple, poly trauma. Crash severity was defined as the most severe injury sustained by any occupant in the crash [16], severe or not severe [31], by using different categories of crash modes (e.g. head-on, rollover) [18] or by the costs of repairing the vehicle [32].

Associations between drug use and injury or accident severity

The associations reported between drug use and injury or accident severity seem to be inconsistent. However, some studies examined the effects of drug use in general [15–19, 23–26, 28–30, 32], whereas other studies differentiated between the different classes of drugs [1, 14, 20–22, 27, 31]. To gain more insight in the study results, a selection of those references included in Table 1, presenting results expressed as relative risk (RR) or odds ratio (OR), have been selected. Table 2 shows the associations between drug use and injury or accident severity. Presented are the first author and the year of publication and the RR or OR (95 % CI) relevant to the association between drug use and injury or accident severity.

Discussion

The study population of the studies reporting on the relationship between drug use and injury or accident severity varied from all crash-involved drivers (injured and not injured), patients admitted to a trauma center (including crash involved drivers) to fatally crash involved drivers. The most frequently applied design is the cross-sectional study. In general, exposure assessment was performed by using toxicological results but, in a few studies, prescription data, police officers' observations or questionnaires were used. Some of the epidemiologic studies seem to present conflicting results with respect to the relationship between drug use and injury or accident severity. The question is whether or not discrepancies can be explained by differences in methodological factors such as outcome variable, study population or exposure measure.

The variety of methods used to express the outcome of interest hampers a comparison between results. The AIS has been developed for motor vehicle accidents (blunt) trauma victims and is an anatomically-based score that describes injuries on a scale of 1 (minor) to 6 (fatal), used to score an individual injury. MAIS is the Maximum Abbreviated Injury Severity Score. The ISS divides the body into six different injury regions. Injuries in each body region are given an AIS score. The ISS is determined by summing the squares of the highest AIS rating (up to 5) for each of the three most severely injured body areas. As a consequence ISS can assume values between zero and 75 [33, 34]. ASCOT is a scoring system for survival probability and uses both anatomical and physiological measures. It considers anatomy, physiology, age, blunt and penetrating trauma [35–37]. Comparing the

Table 2 The association between drug use and injury or accident severity expressed as RR or OR (95 CI%).

	Barbone F 1998				**Kim K 1995**	
Drug	**Accident risk, no injury**	**Accident risk, slight injury**	**Accident risk, serious injury**	**Accident risk, fatal injury**	**Odds multiplier for first stage logit model predicting crash type**	**Odds multiplier for the second stage logit model predicting injury severity**
AMP	–	–	–	–	–	–
BAR	–	–	–	–	–	–
BZD	OR 1.50 (1.12–2.02)	OR 2.12 (1.02–4.38)	OR 1.36 (0.40–4.58)	OR 65.04 (3.11–>1000)	–	–
CAN	–	–	–	–	–	–
COC	–	–	–	–	–	–
METH	–	–	–	–	–	–
OPI	–	–	–	–	–	–
propoxyphene	–	–	–	–	–	–
SSRI	OR 0.89 (0.53–1.47)	OR 0.60 (0.20–1.75)	OR 1.61 (0.21–12.3)	–	–	–
TCA	OR 1.07 (0.81–1.43)	OR 0.59 (0.31–1.13)	OR 1.20 (0.49–2.90)	–	–	–
no alcohol or drugs	–	–	–	–	head on: 0.507; rollover: 0.241	possible or non-incapacitating: 0.717; incapacitating: 0.532; fatal: 0.473
alcohol and/or drugs	–	–	–	–	head on: 1.972; rollover: 4.145	possible or non-incapacitating: 1.395; incapacitating: 1.879; fatal: 2.113
any drug	–	–	–	–	–	–

EtOH = ethanol, AMP = amphetamines, BAR = barbiturates, BZD140 = benzodiazepines, CAN = cannabinoids, COC = cocaine,

METH = methadone, OPI = opiates, TCA = tricyclic antidepressants; SSRI = selective serotonin-reuptake inhibitors

Table 2 (*continued*)

	Meulemans A 1998*			**Singleton M 2004**	**Smink BE 2005**	**Vaez M 2005**
Drug	**ISS > 16**	**AS-COT < 50%**	**death**	**injury severity level**	**accident severity**	**injury severity**
AMP	RR 1.73 (0.91–3.90)	RR 3.98 (1.28–13.1)	RR 2.66 (0.95–7.70)	–	OR 0.3 (0.1–0.7)	–
BAR	RR 1.42 (0.23–4.70)	RR 2.05 (0.00–15.2)	RR 3.51 (0.86–14.1)	–	OR 2.6 (0.2–26.4)	–
BZD	RR 1.66 (1.18–2.81)	RR 1.48 (0.51–4.07)	RR 2.01 (1.04–4.09)	–	OR 0.4 (0.2–0.7)	–
CAN	RR 1.89 (1.29–3.51)	RR 1.87 (0.45–5.77)	RR 2.46 (1.16–5.58)	–	OR 0.7 (0.4–1.2)	–
COC	RR 1.21 (0.04–12.1)	RR 3.81 (0.01–31.3)	RR 2.04 (0.00–15.9)	–	OR 0.4 (0.2–0.7)	–
METH	RR 3.40 (0.41–36.9)	–	RR 11.7 (3.14–141)	–	–	–
OPI	medical: RR 0.50 (0.22–1.21); morphine: RR 3.40 (0.84–4.69)	morphine: RR 1.29 (0.27–9.15)	morphine: RR 2.30 (0.82–4.55)	–	OR 1.6 (0.7–3.9)	–
propoxyphene	RR 2.12 (0.00–26.8)	–	RR 7.2 (0.11–101)	–	–	–
SSRI	–	–	–	–	–	–
TCA	–	–	–	–	–	–
no alcohol or drugs	–	–	–			
alcohol and/or drugs	–	–	–	OR adj. 1.43 (1.31–1.55)	OR 0.6 (0.3–1.0)	OR 3.26 (2.45–4.27)
any drug				–	OR 0.6 (0.4–1.0)	–

RR = Relative Risk: OR = Odds Ratio; 95% Confidence Interval in brackets

ISS = Injury Severtiy Score; ASCOT = A Severity Characterization of Trauma, survival probability

* results with respect to severe cranial or spinal trauma and severe thoracic trauma are not presented

results between studies is difficult because of the lack of consistency in the severity cut off points or the number of categories used. In addition, the statistical methods used to study the relationship between drug use and injury severity measure vary, which may influence outcome. For example, ISS may be treated as a continuous, normally distributed variable as well as a categorical variable [38].

In epidemiological studies, potential confounders, which may be both a risk factor for injury or accident severity and associated with drug use (e.g. health status, gender, age, driving frequency) should be taken into account, but data might be difficult to collect. Characteristics other than alcohol or drugs which have been associated with increased accident severity are, e.g., seat belt use, speed at time of crash, vehicle weight or overweight of the occupants [18, 25, 29, 39, 40]. Data were not always adjusted for those characteristics or for alcohol and/or drug consumption patterns. Complicating factors in determining the influence of drug use on outcome include the variable doses of illicit drugs with an unknown pattern of use, inter-individual variation in response to a given dose, and tolerance. In case of medicinal drug use, the availability of exposure data based on medication records may help to control for bias by previous exposure to drugs.

In most studies, exposure assessment was performed by toxicological analysis. The validity of toxicological results as an exposure measure depends on the drug test panel and the cut-off values applied, the sensitivity and specificity of the analytical methods used, the matrix analysed, and the time period between accident and sampling. Due to medical assistance after a severe accident, the time course may increase between the accident and blood sampling for drug analysis, leading to false negative test results. As a result, the risk estimates will artificially decrease. For most effects of medicinal or illicit drugs, concentration–effect relationships exist. The severity of a car accident may be influenced by impairment and, as a result, may depend on the concentration of the drug that is present in blood. This concentration may drop in the period of time and blood sampling, e.g., when the driver leaves the site of the accident or when the driver is transported to a hospital. In most studies, drug concentrations have not been determined, except for alcohol. It is possible that the mere presence of a drug is not a good predictor for the severity of an accident. This would necessitate concentration measurements in future studies. The presence of a drug or its metabolite in urine is not always an indication of recent drug use. For example, after cannabis use the metabolite THC-COOH may be present in urine for several weeks after the last intake, depending on the pattern of use. If recent drug use is related to more severe injury, the use of urine samples might cover up this relationship.

Another question is whether blood sampling occurs more or less frequently in drivers involved in more severe accidents. This may lead to selection bias. If the frequency of blood sampling were higher in drivers involved in more severe accidents, this would lead to relatively more negative results in severe accidents compared to less severe accidents and thus the odds ratio would artificially decrease. If the frequency of blood sampling were lower in drivers involved in more severe accidents, this would lead to relatively more positive results in severe accidents compared to less severe accidents and thus the odds ratio would artificially increase.

International guidelines to harmonize research related to the effects of psychoactive drugs on injury or accident severity could be very helpful to acquire more univocal results. Injury and accident severity measures should be compared to be able to select the best scoring system [36, 41], and methodological issues should be harmonized.

Conclusions

Evidence is growing that alcohol is not only associated with an increased risk of accidents but also with increased injury and/or accident severity, although conflicting study results have been published [5–8]. The influence of psychoactive drugs other than alcohol on injury and/or accident severity is not clear; the effects reported in the literature are controversial. Some discrepancies may be explained by differences in methodological factors, e.g., study population, injury or accident severity measures, exposure measures. More research must be done to elucidate the relationship between drug use and injury or accident severity.

Appendix: Characteristics of the individual studies reporting on the relationship between drug use and injury or accident severity.

First author (year of publication)	Country	Study design	Study population	Study period	Outcome variable with respect to injury or accident severity	Substances of interest (determinants)	Exposure assessment
"Benzodiazepine/ Driving" Collaborative Group (1993)	France	case-control	injured crash involved road users admitted to a hospital (n total = 2852): responsible drivers (n = 1599) and non-responsible drivers and pedestrians injured (n = 999)	1989–1990	hospitalization yes/no	EtOH, BZD	toxicological results (plasma)
Barbone F (1998)	UK	within person case cross-over	19 346 drivers involved in a first road-traffic accident, 916 ever users of BZD	1992–1995	injury severity: none, slight, serious, fatal	BZD, TCA, SSRI, other psychoactive drugs	prescription data, results breath test
Broyles RW (2001)	USA	cross-sectional	crash involved drivers (n = 454)	1995	the costs of repairing the passenger cars or four-wheel drive vehicles	EtOH and drugs	unknown (information derived from the Oklahoma Department of Public Safety)
Demetriades D (2004)	USA	cross-sectional	trauma fatalities at an academic Level I trauma center (n = 600 including motor vehicle accident deaths n = 85)	2000–2003	ISS, AIS, spinal injury, vital signs	EtOH, COC, OPI, AMP, phencyclidine	toxicological results (serum, urine)
Deutch SR (2004)	Denmark	cross-sectional	victims of major trauma admitted to a regional trauma centre (n = 417 including road traffic crashes n = 333)	1999–2000	ISS, hospitalization time, mortality	EtOH, BAR, BZD, OPI, AMP, COC, CAN	toxicological results (blood, urine)

Appendix: *(continued)* Characteristics of the individual studies reporting on the relationship between drug use and injury or accident severity.

First author (year of publication)	Country	Study design	Study population	Study period	Outcome variable with respect to injury or accident severity	Substances of interest (determinants)	Exposure assessment
Dissanayake S (2002)	USA	cross-sectional	crash involved drivers, aged 65 or more (crash severitiy n=7637; injury severity n=7371)	1993–1996	injury severity: no injury, possible injury, non-incapacitating injury, incapacitating injury, fatal (within 90 days); crash severity: the most severe injury sustained by any occupant in the crash	EtOH and drugs	unknown (information derived from the Traffic Crash Database)
Jacobson B (1983)	Sweden	case-series	traffic accident victims (drivers, cyclists or pedestrians over the age of 15) treated at two hospitals (n=244)	1976–1980	AIS 1–2; AIS 3–5; AIS 6+	EtOH and other drugs (e.g. BZD)	toxicological results (blood), questionnaire
Kim K (1995)	USA	cross-sectional	crash involved drivers of passengers vehicles (n= ca 4,000, totals not equal across variables because of missing data)	1990	injury severity: no injury, possible or noncapacitating injury, incapacitating injury, fatal injury; crash severity: head-on, rollover, other less severe crash modes	EtOH and drugs	police officers' observatons or statements or toxicological results

EtOH=ethanol; AMP=amphetamines; BAR=barbiturates; BZD = benzodiazepines; CAN=cannabinoids; COC=cocaine; OPI= opiates; TCA=tricyclic antidepressants; SSRI= selective serotonin-reuptake inhibitor; ISS=Injury Severtiy Score; AIS= Abbreviated Injury Scale; MAIS=Maximum Abbreviated Injury Severity; ASCOT=A Severity Characterization of Trauma, survival probability; DRS=Disability Rating Scale; KABCO scale=fatal injury (K), incapacitating injury (A), non-incapacitating evident injury (B), possible injury (C), no injury (O)

Appendix: *(continued)* Characteristics of the individual studies reporting on the relationship between drug use and injury or accident severity.

First author (year of publication)	Country	Study design	Study population	Study period	Outcome variable with respect to injury or accident severity	Substances of interest (determinants)	Exposure assessment
Kirby J (1992)	USA	case-control	injured drivers 15 years of age and older admitted to a trauma service (n=201)	1988	ISS	EtOH, OPI, COC metabolite, AMP, BAR, BZD, CAN	toxicological results (blood, urine)
Kurzthaler I (2003)	Austria	case-control	patients injured in a traffic accident and admitted to the trauma surgery emergency room (n=269)	1995	single trauma (S), multiple trauma (M), polytrauma (P)	EtOH, BZD	toxicological results (blood)
Kurzthaler I (2005)	Austria	case-control	non-fatal injured patients admitted to the trauma surgery emergency room (n=1611)	1995	single trauma (S), multiple trauma (M), polytrauma (P)	EtOH, BZD	toxicological results (blood)
MacDonald T (1999)	UK	within person case cross-over	see Barbone 1998, hospitalised patients with trauma 1993–1995 (risk of trauma)	1992–1995	hospital admission yes/no	see Barbone 1998; in addition the relation between benzodiazepine use and risk of hospitalisation	prescription data
Meulemans A (1998)	Belgium	case-control	drivers, aged at least 14, involved in a traffic accident on a public road and entering by direct admission one of the selected emergency departments	1995–1996	ISS, ASCOT, death, severe cranial or spinal trauma, severe thoracic trauma	EtOH, AMP, BAR, BZD, CAN, COC, OPI, methadone, propoxyphene	toxicological results (blood, urine)

Appendix: *(continued)* Characteristics of the individual studies reporting on the relationship between drug use and injury or accident severity.

First author (year of publication)	Country	Study design	Study population	Study period	Outcome variable with respect to injury or accident severity	Substances of interest (determinants)	Exposure assessment
Rivara FP (1989)	USA	case-control	fatally (n=160) and nonfatally (n=452) injured trauma victims	1986	AIS, ISS	EtOH, marijuana, COC, OPI, BZD	toxicological results (blood, urine)
Singleton M (2004)	USA	cross-sectional	crash involved occupants of vehicles that were reported as having either severe damage or very severe damage (n=75900)	2000–2001	injury severity: killed, hospitalized and ISS ≥ 9, hospitalized and ISS < 9, injured but not hospitalized, no apparent injuries	EtOH, drugs	unknown (information from crash report whether the driver was suspected of driving under the influence of drugs and/or alcohol)
Sjogren H (1997)	Sweden	case-control	fatally injured drivers (n=111) and hospitalized injured motor vehicle drivers (n=130)	1991–1993	MAIS	EtOH, licit drugs (e.g. BZD) and illicit drugs	toxicological results (blood)
Smink BE (2005)	The Netherlands	cross-sectional	crash involved drivers (n=993)	1998–1999	accident severtiy: not severe, severe	EtOH, OPI, AMP, COC, methadone, CAN, BZD, BAR, TCA	toxicological results (blood)

EtOH=ethanol; AMP=amphetamines; BAR=barbiturates; BZD=benzodiazepines; CAN=cannabinoids; COC=cocaine; OPI=opiates; TCA=tricyclic antidepressants; SSRI= selective serotonin-reuptake inhibitor; ISS=Injury Severtiy Score; AIS= Abbreviated Injury Scale; MAIS=Maximum Abbreviated Injury Severity; ASCOT=A Severity Characterization of Trauma, survival probability; DRS=Disability Rating Scale; KABCO scale=fatal injury (K), incapacitating injury (A), non-incapacitating evident injury (B), possible injury (C), no injury (O)

Appendix: *(continued)* Characteristics of the individual studies reporting on the relationship between drug use and injury or accident severity.

First author (year of publication)	Country	Study design	Study population	Study period	Outcome variable with respect to injury or accident severity	Substances of interest (determinants)	Exposure assessment
Stoduto G (1993)	Canada	case-series	seriously non fatally injured motor vehicle collision victims admitted to a Regional Trauma Unit (n=854)	1986–1989	ISS, DRS, length of hospital stay, mortality	EtOH, various licit and illicit drugs (e.g. CAN, COC, BZD, OPI)	toxicological results (blood, urine)
Vaez M (2005)	Sweden	cross-sectional	young Swedish crash involved drivers (n=16178)	1988–2000	crash severity (in term of injury): no injury, minor injury, severe or fatal injury	EtOH, other substances	police's information on suspicion of being under the influence of alcohol/other substances
Waller PF (1997)	USA	cross-sectional	injured crash involved road users presenting to two Emergency Departments (n=894)	1992–1994	officer's judgement of injury (the KABCO scale), MAIS, ISS, hospital admission yes/no	EtOH, COC, CAN, OPI	toxicological results (blood)

EtOH=ethanol; AMP=amphetamines; BAR=barbiturates; BZD = benzodiazepines; CAN=cannabinoids; COC=cocaine; OPI=opiates; TCA=tricyclic antidepressants; SSRI=selective serotonin-reuptake inhibitor; ISS=Injury Severtiy Score; AIS= Abbreviated Injury Scale; MAIS=Maximum Abbreviated Injury Severity; ASCOT=A Severity Characterization of Trauma, survival probability; DRS=Disability Rating Scale; KABCO scale=fatal injury (K), incapacitating injury (A), non-incapacitating evident injury (B), possible injury (C), no injury (O)

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Drugs, Driving and Traffic Safety
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Pharmacokinetics and pharmacodynamics of drugs abused in driving

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Abstract

Driving under the influence of impairing drugs is a prevalent and preventable worldwide problem. Scientists are conducting pharmacodynamic and pharmacokinetic studies to help officials identify drugged drivers and remove them from the roadways. Current approaches for drugs of abuse other than alcohol first determine an estimate of time of use from concentrations of drugs and metabolites in bodily fluids following controlled drug administration. The degree of driving impairment is then suggested based on the time course of effects from pharmacodynamic studies. Reasonable estimates of impairment can be made based on currently available studies for cannabis, cocaine, amphetamines and opioids. Predictive models were published relating cannabinoid concentrations in plasma and whole blood with time of use following various routes of administration and doses. Results of performance tests and driving simulators after controlled cannabis dosing document impairment at various times after use and show that impairment can last up to eight hours for many tasks and 24 hours for complex divided-attention tasks. A few studies on other drugs report expected plasma or oral fluid concentrations with time after drug administration. Degree of impairment is dependant on dose, route of administration, and tolerance. Further pharmacokinetic and pharmacodynamic studies are needed to guide drug concentration interpretation, to develop predictive models for other drugs, and to guide development of science-based drugged driving legislation.

Introduction

Driving under the influence of drugs is a serious and preventable worldwide problem [1]. Drugged drivers must be removed from the roadway and individuals must be educated and deterred from driving while intoxicated. This is accomplished in

part by the judicial systems of countries that have forensic toxicologists identify and quantify drugs and metabolites in biological fluids and estimate their impairing effects. An understanding of the drug's pharmacokinetics is essential to comprehending the relationship between drug concentrations and impairment [1, 2]. The most thoroughly studied drug in traffic safety is alcohol (ethanol), since historically it has been the most prevalent cause of driving accidents [3]. Scientists investigating the absorption, distribution, metabolism and elimination of alcohol following controlled administration found a direct relationship between blood alcohol concentration and poor driving performance [4]. The alcohol model was then applied to other drugs of abuse with less success. Alcohol has different physiochemical characteristics from most other drugs, and is consumed orally, while many drugs of abuse are inhaled or taken intravenously. These important differences and routes of administration affect a drug's pharmacokinetics, its concentration-effect curve, and the interpretation of blood concentrations. Few other drugs important in the accident and traffic safety literature have a linear correlation between drug concentrations and effects, and few have been studied as thoroughly as alcohol. In this chapter, the available data guiding interpretation of drug concentrations of cannabinoids, cocaine, amphetamines and opiates are reviewed.

A common successful approach is to first estimate the time at which drug exposure occurred based on drug and metabolite concentrations following controlled drug administration. Scientific studies of the drug's pharmacodynamic effects are then referenced to link time of drug use with impaired performance. Other approaches include epidemiologic research, especially responsibility analyses that statistically prove that drivers under the influence of a drug have a higher odds ratio for having an accident than drivers on the same road, at the same time, that are not under the influence of drug. Other epidemiological research includes case study analyses, i.e. the Grand Rapids study of the effects of alcohol on driving [5], where large numbers of drivers are stopped, performance is evaluated, and biological specimens sampled. These types of data provide definitive information about impaired driving performance, but are expensive and difficult to conduct, especially if a more invasive specimen collection is required. An important advantage of studying alcohol's effects on driving is that breath concentrations that are less invasive than venipuncture are suitable for estimating blood concentrations, unlike for any other drug class. An exciting new opportunity is available to the field of traffic safety with the advent of sensitive and non-invasive oral fluid drug monitoring. New large-scale epidemiologic driving studies are conducted with oral fluid drug testing providing data on recent drug exposure.

Another challenge in estimating time of drug use is that elimination of drug and metabolites usually follows first order kinetics and is often bi- or multi-phasic. This is a major difference from alcohol, which is eliminated by zero order kinetics. The constant rate of alcohol excretion allows reasonable back extrapolation of drug concentrations from the time of blood collection to the time of an accident or traffic stop. The extrapolated blood alcohol concentration permits estimates of impairment at the time of driving. Since most impaired driving investigations involve a single specimen collected at a known point in time after an incident, and elimination rates are not zero order for most drugs, methods for estimating time of last drug use are

more complex. One approach is to develop empirical functions relating time of use with biological fluid drug and metabolite concentrations, e.g. estimates for last cannabis use [6–8]. Another is to identify the presence of a short-lived metabolite, since finding the biomarker narrows the range for time of last use. An example is the analysis of 6-acetylmorphine in blood for estimating time of heroin use [9, 10]. With a short half-life of only 6–25 min, identifying this analyte suggests recent use. For these reasons, knowledge of a drug's pharmacokinetics following different routes of administration and in alternate matrices, and knowing intra- and inter-subject variability are critical factors for estimating driving impairment.

Cannabinoid Pharmacokinetics

In most jurisdictions cannabis is the second most prevalent drug encountered in traffic safety cases after ethanol [3]. The biology, chemistry, pharmacology and toxicology of the principal psychoactive substance delta-9-tetrahydrocannabinol (THC) have been extensively studied. Although much is known about the pharmacokinetics of cannabinoids in plasma following smoking [7, 11–14], the pharmacokinetics after the drug is ingested by other routes are less well described, as are the pharmacokinetics in blood and oral fluid. The oral route is becoming more important as new THC-containing medications are developed for analgesia, appetite enhancement in AIDS-wasting disease, counteracting spasticity of motor diseases, and emesis following chemotherapy, among many other applications [15]. In addition, oral fluid is becoming the biological matrix of choice for screening for drug impairment at the roadside.

Pharmacokinetics encompasses the absorption of cannabinoids following diverse routes of administration and from different drug formulations, the distribution of analytes throughout the body, the metabolism of cannabinoids by different tissues and organs, the elimination of cannabinoids from the body in the feces, urine, sweat, oral fluid, and hair, and how these processes change over time. Many of the classic studies of cannabinoid pharmacokinetics are from the 1970s and 1980s. Challenges to cannabinoid pharmacokinetic research are low analyte concentrations, rapid and extensive metabolism, and physicochemical characteristics that hinder the separation of drugs of interest from biological matrices and from each other, and lower drug recovery due to adsorption of compounds of interest to multiple surfaces. Much of the earlier data utilized radio-labeled cannabinoids yielding highly sensitive but less specific measurement of individual cannabinoid analytes. Mass spectrometric developments now permit highly sensitive and selective measurement of cannabinoids in a wide variety of biological matrices.

Cannabis sativa contains over 421 different chemical compounds, including over 60 cannabinoids [16–18]. Cannabinoid plant chemistry is far more complex than pure THC. Different effects may be expected due to the presence of additional cannabinoids and other chemicals when cannabis is administered rather than only its most active compound. Eighteen different classes of chemicals, including nitrogenous compounds, amino acids, hydrocarbons, sugars, terpenes, and simple

and fatty acids contribute to cannabis' known pharmacological and toxicological properties. THC is usually present in Cannabis plant material as a mixture of monocarboxylic acids that readily and efficiently decarboxylate upon heating. THC decomposes when exposed to air, heat, or light; exposure to acid can oxidize the compound to cannabinol, a much less potent cannabinoid. In addition, cannabis plants dried in the sun release variable amounts of THC through decarboxylation. During smoking, more than 2000 compounds may be produced by pyrolysis. The focus of this section will be THC, its metabolites 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THCCOOH) [19]. Mechoulam et al. elucidated the structure of THC after years of effort in 1964, opening the way for studies of the drug's pharmacokinetics [20]. THC, containing no nitrogen but with two chiral centers in the trans-configuration, is described by two different numbering systems, the dibenzopyran or delta 9, and the monoterpene or delta 1 system; the dibenzopyran system is employed in this chapter.

Absorption

Smoked administration

Route of drug administration and drug formulation determine the rate of drug absorption. Smoking, the principal route of cannabis administration, provides a rapid and efficient method of drug delivery from the lungs to the brain, contributing to its abuse potential. Intense, pleasurable and strongly reinforcing effects may be produced due to almost immediate drug exposure to the central nervous system. Slightly lower peak THC concentrations are achieved after smoking as compared to intravenous administration [21]. Bioavailability following the smoking route was reported as 2–56 %, due in part to the intra- and inter-subject variability in smoking dynamics that contribute to uncertainty in dose delivery [22–25]. The number, duration and spacing of puffs, hold time and inhalation volume, or smoking topography, greatly influences the degree of drug exposure [26–28]. Expectation of drug reward also may affect smoking dynamics. Cami et al. noted that subjects were able to change their method of smoking hashish cigarettes to obtain higher plasma concentrations of THC when they expected to receive active drug in comparison to placebo cigarettes [29].

A continuous blood withdrawal pump was utilized to capture the rapid absorption of THC and formation of 11-OH-THC and THCCOOH during cannabis smoking [14]. The disposition of THC and its metabolites was followed over seven days after smoking a single placebo, 1.75 % or 3.55 % THC cigarette. Plasma concentrations were determined by gas-chromatography mass spectrometry (GC-MS). THC was detected in the plasma immediately after the first cigarette puff and was accompanied by the onset of cannabinoid effects [13]. Mean ± SD THC concentrations of 7.0 ± 8.1 μg/L and 18.1 ± 12.0 μg/L were observed following the first inhalation of a low (1.75 % THC, approximately 16 mg) or high (3.55 % THC, approximately 30 mg) dose cigarette, respectively [14]. Concentrations increased rapidly, reaching

mean peaks of 84.3 μg/L (range 50 to 129) and 162.2 μg/L (range 76 to 267) for the low and high dose cigarette, respectively. Peak concentrations occurred at 9.0 min, prior to initiation of the last puff sequence at 9.8 min. Despite a computer-paced smoking procedure that controlled the number of puffs, length of inhalation, hold time and time between puffs, there were large inter-subject differences in plasma THC concentrations due to differences in the depth of inhalation as participants titrated their THC dose (Fig. 1). Mean THC concentrations were approximately 60% and 20% of peak concentrations 15 and 30 minutes post smoking, respectively. Within 2 h, plasma THC concentrations were at or below 5 μg/L. The time of detection of THC (GC/MS lower limit of quantification [LOQ] = 0.5 μg/L) varied from 3 to 12 h after the low dose and from 6 to 27 h after the high dose cannabis cigarette.

Mean peak plasma 11-OH-THC concentrations were 6.7 and 7.5 μg/L for the low and high doses, respectively. THCCOOH concentrations gradually increased and peaked between 0.54 and 4 h (mean 1.9 h) at mean (range) concentrations of 24.5 (15–54) and 54.0 (22–101) μg/L, respectively (Fig. 2).

Similar mean THC C_{max} concentrations were reported in specimens collected immediately after cannabis smoking was completed. Mean peak THC concentrations were 94.3, 107.4 and 155.1 μg/L THC after smoking a single 1.32, 1.97, or 2.54% THC cigarettes, respectively [19]. Other reported peak THC concentrations ranged between 45.6 to 187.8 μg/L following smoking of an approximate 1% THC ciga-

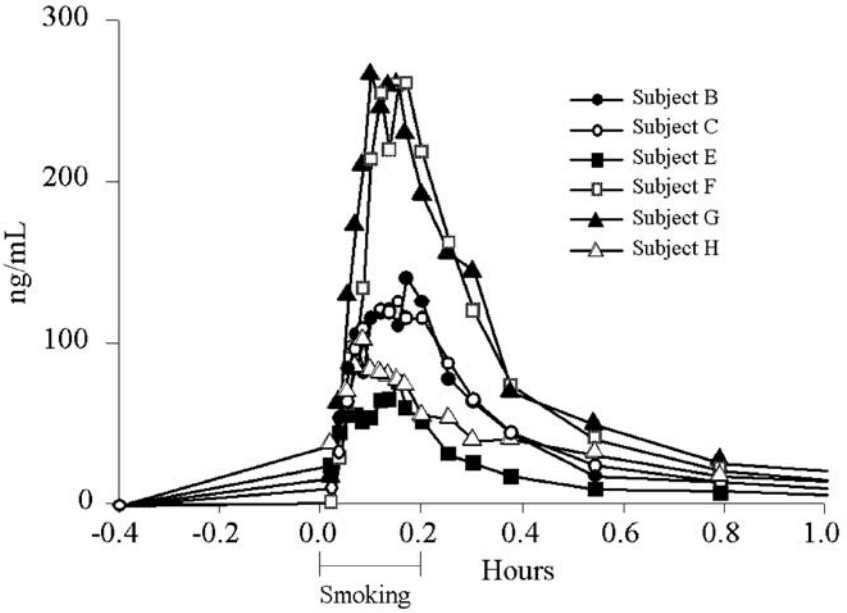

Figure 1 Plasma delta-9-tetrahydrocannabinol (THC) concentrations in six subjects after each smoked a 3.55% THC cigarette.

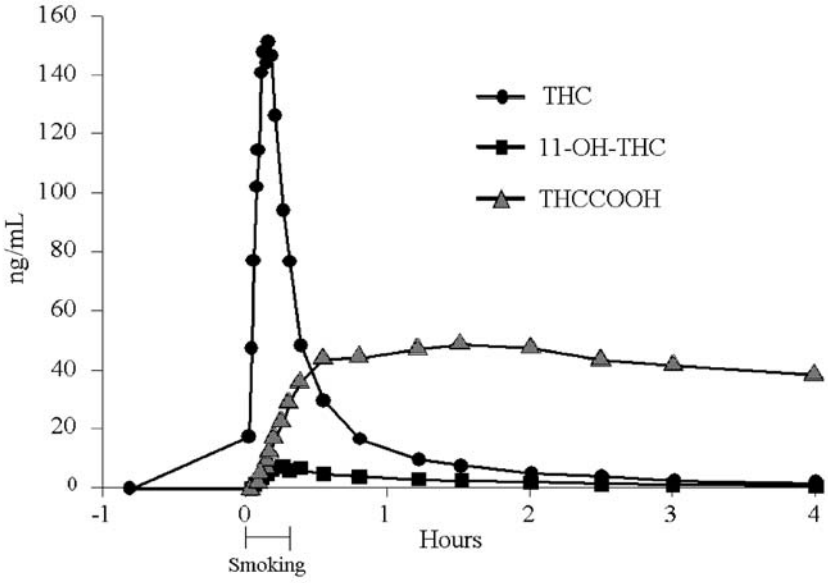

Figure 2 Mean plasma delta-9-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH) concentrations in six subjects after smoking a single 3.55 % THC cigarette.

rette [30] and 33 to 118 μg/L three minutes after ad lib smoking of an approximate 2 % THC cigarette [21]. Many individuals prefer the smoked route, not only for its rapid drug delivery, but also the ability to titrate their dose.

Oral administration

There are fewer studies on the disposition of THC and metabolites after oral as compared to the smoked route of cannabis administration. THC is readily absorbed due to its high octanol/water coefficient, estimated to be between 6000 and over nine million by different technologies [31]. The advantages of cannabinoid smoking are offset by the harmful effects of cannabinoid smoke; hence, smoking is generally not recommended for therapeutic applications. Synthetic THC (dronabinol) preparations are usually taken orally, but may also be administered rectally. In addition, abuse of cannabis by the oral route is also common. Absorption is slower when cannabinoids are ingested with lower, more delayed peak THC concentrations [32, 33]. Dose, route of administration, vehicle, and physiological factors such as absorption and rates of metabolism and excretion can influence drug concentrations in circulation. Perez-Reyes et al. described the efficacy of five different vehicles used in the oral administration of THC in gelatin capsules [34]. Glycocholate and

sesame oil improved the bioavailability of oral THC; however, there was considerable variability in peak concentrations and rates of absorption, even when the drug was administered in the same vehicle. Oral THC bioavailability was reported to be 10 % to 20 % by Wall et al. [35]. In their study, participants were dosed with either 15 (women) or 20 mg (men) THC dissolved in sesame oil and contained in gelatin capsules. THC plasma concentrations peaked approximately 4 to 6 h after ingestion of 15 to 20 mg of THC in sesame oil. A percentage of the THC was radio-labeled; however, investigators were unable to differentiate labeled THC from its labeled metabolites. Thus, THC concentrations were overestimated.

Possibly a more accurate assessment of oral bioavailability that utilized GC/MS to quantify THC in plasma samples was reported by Ohlsson et al. [21]. Peak THC concentrations ranged from 4.4 to 11 μg/L and occurred 1 to 5 h following ingestion of 20 mg of THC in a chocolate cookie. Oral bioavailability was estimated to be 6 %. Slow rates of absorption and low THC concentrations occur after oral administration of THC or cannabis. Several factors may account for the low oral bioavailability of 4–20 % (as compared to intravenous drug administration) including variable absorption, degradation of drug in the stomach and significant first pass metabolism to active 11-OH-THC and inactive metabolites in the liver.

Recently, there has been renewed interest in oral THC pharmacokinetics due to the therapeutic value of orally administered THC. In a study of THC, 11OH-THC and THCCOOH concentrations in 17 volunteers after a single 10 mg Marinol® capsule, mean peak plasma THC concentrations of 3.8 μg/L (range 1.1–12.7), 11-OH-THC 3.4 μg/L (range 1.2–5.6), and THCCOOH 26 μg/L (range 14–46) were observed one to two hoursafter ingestion [36]. Similar THC and 11-OH-THC concentrations were observed with consistently higher THCCOOH concentrations. Interestingly, two peak THC concentrations frequently were observed due to enterohepatic circulation. The onset, magnitude, and duration of pharmacodynamic effects generally occur later, are lower in magnitude and have a delayed return to baseline when THC is administered by the oral as compared to the smoked route of administration [37, 38].

In addition, THC-containing foods, i.e. hemp oil, hemp beer, and other products, are commercially available for oral consumption. Hemp oil is produced from cannabis seed and is an excellent source of essential amino acids and omega-linoleic and linolenic fatty acids. THC content is dependent upon the effectiveness of cannabis seed cleaning and oil filtration processes. Hemp oil of greater than 300 mg THC/g was available in the US and up to 1500 mg THC/g in Europe. Currently, hemp oil THC concentrations in the US are low, reflecting the efforts of manufacturers to reduce the amount of THC in hemp oil products.

In a recent controlled cannabinoid administration study of THC-containing hemp oils and dronabinol, the pharmacokinetics and pharmacodynamics of oral THC were evaluated. Up to 14.8 mg of THC was ingested by six volunteers each day in three divided doses with meals for five consecutive days [39]. There was a 10-day washout phase between each of the five dosing sessions. THC was quantified in plasma by solid-phase extraction followed by positive chemical ionization GC-MS. THC and 11-OH-THC were rarely detected in plasma following the

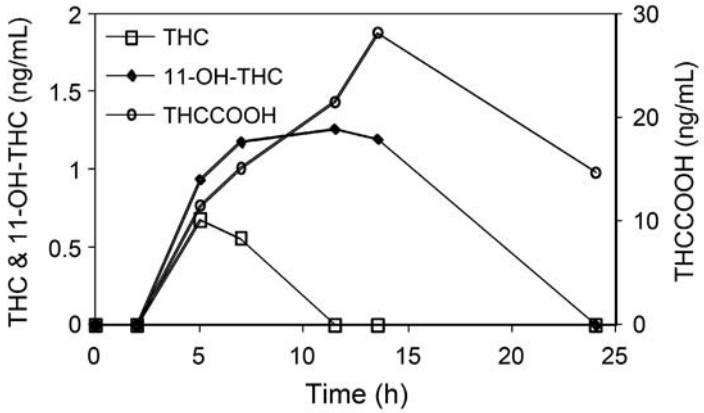

Figure 3 Mean plasma delta-9-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH) concentrations in six subjects after each ingested two oral 2.5 mg dronabinol capsules.

two lowest doses 0.39 and 0.47 mg/day THC, while peak plasma concentrations of less than 6.5 μg/L THC, less than 5.6 μg/L 11-OH-THC, and less than 43.0 μg/L THCCOOH were found after the two highest THC doses of 7.5 and 14.8 mg/day (Fig. 3). Interestingly, THCCOOH concentrations after the 7.5 mg/day dronabinol dose were greater than or equal to those of the high potency 14.8 mg/day hemp oil dose. This could be due to the dronabinol formulation that afforded greater protection from degradation in the stomach due to encapsulation and perhaps improved bioavailability of THC in sesame oil, the formulation of synthetic THC or dronabinol. Plasma THC and 11-OH-THC concentrations fell below the method's LOQ of 0.5 μg/L by 25 hours, while THCCOOH was still measurable for more than 50 hours after the last dose of the higher concentration hemp oils.

Distribution

THC concentrations decrease rapidly after the end of smoking due to its rapid distribution into tissues and metabolism in the liver. THC is highly lipophilic and is initially taken up by tissues that are highly perfused, such as lung, heart, brain, and liver. In animals after i.v. administration of labeled THC, higher levels of radioactivity are present in the lung than in other tissues [40]. Adams and Martin determined that a THC dose of 2 to 22 mg is necessary to produce pharmacological effects in humans [41]. Assuming that 10–25% of the available THC enters the circulation during smoking, the actual dose required was estimated as 0.2 to 4.4 mg. Furthermore, only about 1% of the dose at peak concentration was found in the brain, indicating that only 2–44 μg of THC penetrates the brain. Chiang et al.

estimated that equilibration was reached between plasma and tissue THC approximately 6 h after an intravenous THC dose [42].

Metabolism of THC to 11-OH-THC, THCCOOH and other analytes also contributes to the reduction of THC in the blood. Perez-Reyes et al. compared the pharmacokinetics and pharmacodynamics of tritiated THC and 11-OH-THC in 20 male volunteers [43]. Although equal doses produced equal psychoactive effects, drug effects were perceived more rapidly after 11-OH-THC than after THC. In addition, 11-OH-THC left the intravascular compartment faster than THC. These data suggest that 11-OH-THC diffuses into the brain more readily than THC. Other possible explanations include lower plasma protein binding of 11-OH-THC or enhanced crossing of the blood-brain barrier by the hydroxylated metabolite. Further support for the faster penetration of brain by 11-OH-THC is found in studies documenting a more rapid diffusion of 11-OH-THC than THC into the brains of mice [43].

THC's volume of distribution (V_d) is large, approximately 10 L/kg, despite the fact that it is 95–99% protein bound in plasma, primarily to lipoproteins [44, 45]. More recently, with the benefit of advanced analytical techniques, THC's steady state V_d was found to be 3.4 L/kg [46]. Less highly perfused tissues, including fat, accumulate drug more slowly as THC redistributes from the vascular compartment [47]. With prolonged drug exposure, THC concentrates in fat and may be retained for extended periods of time [48, 49]. It is suggested that fatty acid conjugates of THC and 11-OH-THC may be formed, increasing the stability of these compounds in fat [46].

Distribution of THC into peripheral organs and brains was found to be similar in THC tolerant and non-tolerant dogs [50]. In addition, Dewey et al. found that tolerance to the behavioral effects of THC in pigeons was not due to decreased uptake of cannabinoids into brain [51]. Tolerance also was evaluated in humans by Hunt and Jones [44]. Tolerance in humans developed during oral administration of 30 mg of THC every four hours for 10 to 12 days. Few pharmacokinetic changes were noted

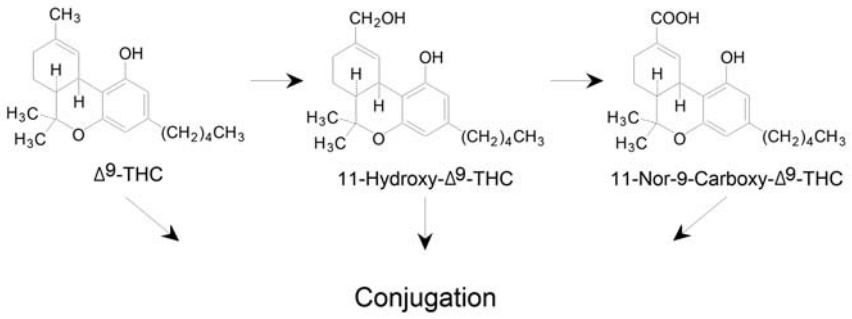

Figure 4 The primary phase I and phase II cannabinoid metabolism in humans after delta-9-tetrahydrocannabinol (THC) administration.

during chronic administration, although average total metabolic clearance and initial apparent volume of distribution increased from 605 to 977 ml/min and from 2.6 to 6.4 L/kg, respectively. The pharmacokinetic changes observed after chronic oral THC could not account for the observed behavioral and physiologic tolerance, suggesting rather that tolerance was due to pharmacodynamic adaptation.

Metabolism

The primary metabolic routes and metabolites of THC are depicted in Figure 4. THC is metabolized primarily by the liver; hydroxylation of THC at C9 by the hepatic cytochrome P450 enzyme system leads to production of the equipotent metabolite, 11-OH-THC [52], believed by early investigators to be the true psychoactive analyte [40]. Cytochrome P450 2C9, 2C19 and 3A4 are involved in the oxidation of THC [52]. More than 100 THC metabolites including di- and tri-hydroxy compounds, ketones, aldehydes and carboxylic acids have been identified [46, 47, 53]. Although 11-OH-THC predominates as the first oxidation product, significant amounts of 8-beta-OH-THC and lower amounts of the 8-alpha-OH-THC are formed. Much lower plasma 11-OH-THC concentrations (approximately 10 % of THC concentrations) are found after cannabis smoking than after oral administration [35]. Peak 11-OH-THC concentrations occurred approximately 13 minutes after the start of smoking [14]. Bornheim et al. reported that 11-OH-THC and 8-beta-OH-THC were formed at the same rate in human liver microsomes, with smaller amounts of epoxy-hexahydrocannabinol, 8-alpha-OH-THC and 8-keto-THC [54]. Cytochrome P450 2C9 is believed to be primarily responsible for the formation of 11-OH-THC, whereas P450 3A catalyzes the formation of 8-beta-OH-THC, epoxy hexahydrocannabinol and other minor metabolites. Less than a five-fold variability in 2C9 rates of activity were observed, while much higher variability was noted for 3A. Dihydroxylation of THC yields 8-beta-11-di-OH-THC. Excretion of 8-beta-11-di-OH-THC in urine was reported to be a good biomarker for recent cannabis use [55].

Oxidation of the active 11-OH-THC produces the inactive metabolite, THCCOOH [40, 56]. THCCOOH and its glucuronide conjugate are the major end products of biotransformation in most species, including man [53, 57]. THCCOOH concentrations gradually increase and are greater than THC concentrations 30 to 45 minutes after the end of smoking [58]. After ingestion of a single 10 mg oral dose of Marinol®, plasma THCCOOH concentrations were higher than THC and 11-OH-THC concentrations as early as one hour after dosing [36]. Unlike after smoking, THC and 11-OH-THC concentrations are similar after oral THC administration. Phase II metabolism of THCCOOH involves addition of glucuronic acid, and less commonly, sulfate, glutathione, amino acids and fatty acids *via* the C11 carboxyl group. The phenolic hydroxyl group may be a target as well. It is also possible to have two glucuronic acid moieties attached to THCCOOH, although steric hindrance at the phenolic hydroxyl group could be a factor. Addition of the glucuronide group improves water solubility facilitating excretion, but renal clearance of these

polar metabolites is low due to extensive protein binding [44]. No significant differences in metabolism between men and women have been reported [35].

After the initial distribution phase, the rate-limiting step in the metabolism of THC is its redistribution from lipid depots into blood [50]. Lemberger et al. suggested that frequent cannabis smoking could induce THC metabolism [59]. However, later studies did not replicate this finding [24, 53].

Elimination

Within five days, a total of eighty to ninety percent of a THC dose is excreted, mostly as hydroxylated and carboxylated metabolites [47, 57]. More than 65 % is excreted in the feces, with approximately 20 % eliminated in the urine [35]. Numerous acidic metabolites are found in the urine, many of which are conjugated with glucuronic acid to increase their water solubility. The primary urinary metabolite is the acid-linked THCCOOH glucuronide conjugate [60], while 11-OH-THC predominates in the feces [47]. The concentration of free THCCOOH and the cross-reactivity of glucuronide-bound THCCOOH enable cannabinoid immunoassays to be performed directly on non-hydrolyzed urine, but confirmation and quantification of THCCOOH is usually performed after alkaline hydrolysis or β-glucuronidase hydrolysis to free THCCOOH for measurement by GC/MS. It was generally thought that little to no THC or 11-OH-THC was excreted in the urine, but later studies, discussed below, found that they are excreted as O-glucuronides [61, 62].

Terminal elimination half-lives of THCCOOH

THC and THCCOOH do not have a constant half-life during elimination. The initial phase is more rapid than terminal elimination. To determine an accurate terminal half-life, it is important to have sensitive procedures that measure low cannabinoid concentrations and blood specimens must be collected over an extended period. Many studies utilized short sampling intervals of 24 to 72 h that underestimate terminal THC and THCCOOH half-lives. The slow release of THC from lipid storage compartments and significant enterohepatic circulation contribute to THC's long terminal half-life in plasma, reported as greater than 4.1 days in chronic cannabis users [63]. Isotopically-labeled THC and sensitive analytical procedures were used to obtain this drug half-life. Garrett and Hunt reported that 10–15 % of the THC dose is enterohepatically circulated in dogs [50]. Johansson et al. reported a THCCOOH plasma elimination half-life up to 12.6 days in a chronic cannabis user when monitoring THCCOOH concentrations for four weeks [64]. Mean plasma THCCOOH elimination half-lives were 5.2 ± 0.8 and 6.2 ± 6.7 days for frequent and infrequent cannabis users, respectively. Similarly, when sensitive analytical procedures and sufficient sampling periods were employed for determining the terminal urinary excretion half-life of THCCOOH, it was estimated to be three to four days

[65]. Urinary THCCOOH concentrations drop rapidly until approximately 20 to 50 μg/L, and then decrease at a much slower rate. No significant pharmacokinetic differences between chronic and occasional users have been substantiated [42].

Percent THC Dose Excreted as Urinary THCCOOH

An average of 93.9 ± 24.5 μg THCCOOH (range 34.6–171.6) was measured in urine over a seven day period following smoking of a single 1.75 % THC cigarette containing approximately 18 mg THC [66]. The average amount of THCCOOH excreted in the same time period following the high dose (3.55 % THC containing approximately 34 mg THC) was 197.4 ± 33.6 μg (range 107.5–305.0). This represented an average of only 0.54 ± 0.14 % and 0.53 ± 0.09 % of the original amount of THC in the low and high dose cigarettes, respectively. The small percentage of total dose found in urine as THCCOOH is not surprising considering the many factors that influence THCCOOH excretion after smoking. Prior to harvesting, cannabis plant material contains little active THC. When smoked, THC carboxylic acids spontaneously decarboxylate to produce THC with nearly complete conversion upon heating. Pyrolysis of THC during smoking destroys additional drug. Drug availability is further reduced by loss of drug in the side-stream smoke and drug remaining in the unsmoked cigarette butt. These factors contribute to high variability in drug delivery by the smoked route. It is estimated that the systemic availability of smoked THC is approximately 8 to 24 % and that bioavailability depends strongly upon the experience of the cannabis user [21, 30, 67]. THC bioavailability is reduced due to the combined effect of these factors; the actual available dose is much lower than the amount of THC and THC precursor present in the cigarette. Most of the THC dose is excreted in the feces (30 to 65 %), rather than in the urine (20 %) [35, 68]. Another factor affecting the low amount of recovered dose is measurement of a single metabolite. Numerous cannabinoid metabolites are produced in humans as a result of THC metabolism, most of which are not measured or included in the % dose excreted calculations when utilizing GC/MS.

Specimen preparation for cannabinoid testing frequently includes a hydrolysis step to free cannabinoids from their glucuronide conjugates. Most GC/MS confirmation procedures in urine measure total THCCOOH following either an enzymatic hydrolysis with β-glucuronidase, or more commonly, an alkaline hydrolysis with sodium hydroxide. Alkaline hydrolysis appears to efficiently hydrolyze the ester THCCOOH glucuronide linkage.

Urinary biomarkers of recent cannabis use

Significantly higher concentrations of THC and 11-OH-THC in urine are observed when *Escherichia coli* β-glucuronidase is employed in the hydrolysis method compared to either *Helix pomatia* β-glucuronidase or base [61, 62]. THC and 11-OH-

THC primarily are excreted in urine as glucuronide conjugates that are resistant to cleavage by alkaline hydrolysis and by enzymatic hydrolysis procedures employing some types of β-glucuronidase. Kemp et al. demonstrated that β-glucuronidase from *E. coli* was needed to hydrolyze the ether glucuronide linkages of the active cannabinoid analytes. Mean THC concentrations in urine specimens from seven subjects collected after each had smoked a single 3.58% marijuana cigarette was 22 μg/L using the *E. coli* β-glucuronidase hydrolysis method while THC concentrations using either *H. pomatia* β-glucuronidase or base hydrolysis methods were near zero [61, 62]. Similar differences were found for 11-OH-THC with a mean concentration of 72 μg/L from the *E. coli* method and concentrations less than 10 μg/L from the other methods. The authors suggested that finding THC and/or 11-OH-THC in the urine might provide a reliable marker of recent cannabis use, but adequate data from controlled drug administration studies were not yet available to support or refute this observation. Using a modified analytical method with *E. coli* β-glucuronidase, we have analyzed hundreds of urine specimens collected following controlled THC administration. We found that 11-OH-THC may be excreted in the urine of chronic cannabis users for a much longer period of time, beyond the period of pharmacodynamic effects and performance impairment. Additional research is necessary to determine the validity of estimating time of cannabis use from THC and 11-OH-THC concentrations in urine.

Chronic cannabis use

Most THC plasma data were collected following acute exposure; less is known of plasma THC concentrations in frequent users. Peat reported THC, 11-OH-THC, and THCCOOH plasma concentrations in frequent cannabis users of 0.86±0.22, 0.46±0.17 and 45.8 ±13.1 μg/L, respectively, a minimum of 12 h after the last smoked dose [69]. No difference in terminal half-life in frequent or infrequent users was observed. Johansson et al. administered radiolabeled THC to frequent cannabis users and found a terminal elimination half-life of 4.1 days for THC in plasma due to extensive storage and release from body fat [63]. Currently, studies are in progress to examine cannabinoid concentrations in blood from daily cannabis users during monitored abstinence. Preliminary findings for 28 daily cannabis users during residence on a closed research unit with no access to drug revealed that whole blood THC concentrations remained above the method LOQ of 0.25 μg/L in 15 participants for more than 24 h [70]. Six participants' whole blood specimens were still above this limit after seven days of monitored abstinence with three of the six having THC greater than 1 μg/L. It should be stressed that these concentrations were only found in individuals who were long-term daily cannabis smokers, with less than daily cannabis smokers producing negative whole blood tests within 8 h of cannabis use. Also, the 0.25 μg/L LOQ that was achieved by 2D GCMS with cryofocusing [71] is much lower than most analytical procedures' limit and lower than most laboratories' cannabinoid reporting threshold.

Cannabinoids in oral fluid

Oral fluid is one alternative matrix that is being investigated to determine recent drug use. There are currently problems examining cannabinoids in oral fluid including THC contamination during smoking, low concentrations of THC and THCCOOH and adsorption of cannabinoids to collection devices. However, with solutions to these problems, oral fluid may be useful for determining recent cannabis use. Thirty minutes after smoking, oral fluid/plasma THC concentration ratios are near 1.0 (Fig. 5) [72].

Models for predicting time of cannabis use

Empirical methods that accurately predict time of cannabis exposure would provide valuable information in establishing the role of cannabis as a contributing factor to events under investigation. Huestis et al. determined the plasma THC, 11-OH-THC, and THCCOOH concentrations for six occasional cannabis users for 168 h after each smoked a 1.75 % and separately a 3.55 % THC cigarette [6, 14]. Mean concentrations for the first 4 h after the higher dose are shown in Figure 2. Since plasma THC and THCCOOH concentrations were a function of time from the beginning of smoking cannabis, one could develop empirical formulas for predicting time of cannabis use based on analysis of a single plasma specimen for these analytes [6]. Plasma THC and THCCOOH concentrations from their study were used to develop

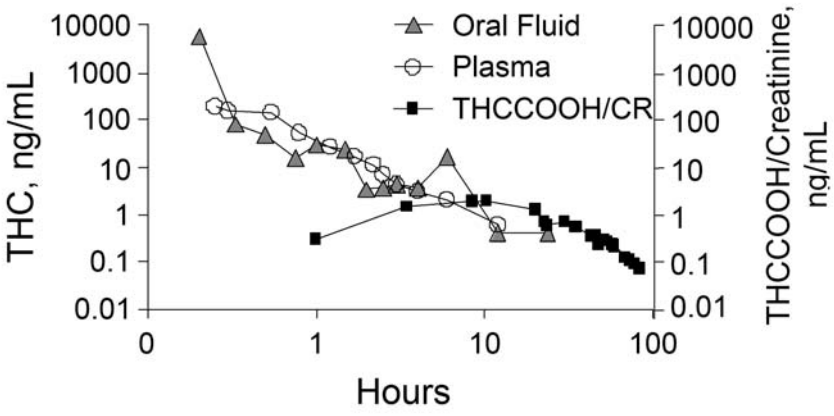

Figure 5 Mean oral fluid and plasma delta-9-tetrahydrocannabinol (THC) concentrations (μg/L) in six subjects after each smoked one 3.55 % THC cigarette. Creatinine normalized urine 11-nor-9-carboxy-THC (THCCOOH) concentrations (μg/g) are displayed for comparison.

two mathematical models. Model I determined time estimates from plasma THC concentrations and Model II from plasma concentration ratios of THCCOOH/THC. The formulas are reproduced below with T representing the elapsed time in hours between the beginning of cannabis smoking and blood collection, and CI representing the 95% confidence interval for the estimate of T. The subscripts 1 and 2 refer to Models I and II, respectively, and brackets indicate the concentrations of THC or THCCOOH in μg/L:

Model I: $\log T = -0.698 \log [THC] + 0.687$

$$\log CI_1 = \log T + 1.975 \sqrt{0.030\left\{1.006 + \frac{\left(\log[THC] - 0.996\right)^2}{89.937}\right\}}$$

Model II: $\log T = (0.576 \log [THCCOOH]/[THC]) - 0.176$

$$\log CI_2 = \log T + 1.975 \sqrt{0.045\left\{1.006 + \frac{\left(\log [THCCOOH]/[THC] - 0.283\right)^2}{123.420}\right\}}$$

The models predict last cannabis use within a specified interval of time. The magnitude of the interval is smaller when the elapsed time between cannabis use and blood collection is shorter. Plots of the model equations are displayed with actual data points in Figure 6. Models were applied to all published studies at the time that included plasma concentrations; both models correctly predicted times of cannabis exposure within 95% confidence intervals for more than 90% of specimens evaluated.

More recently the validation of these predictive models was extended to include estimation of time of use after multiple doses of THC and at low THC concentrations (0.5 to 2 μg/L), situations that were not included in original model development [7]. Thirty-eight cannabis users each smoked a 2.64% THC cigarette in the morning and 30 also smoked a second cigarette in the afternoon. Blood specimens (n = 717) were collected at intervals after smoking and plasma THC and THCCOOH concentrations measured by GC/MS. Predicted times of cannabis smoking, based on each model, were compared to actual smoking times. For over 90% of cases, the observed smoking time fell within the confidence interval predicted by each model. Results are shown in Table 1. Model I was less accurate with primarily overestimates that benefit the accused. Following single doses, Model II had primarily underestimates that are less favorable in forensic testing since they tend to predict earlier cannabis use that could be misinterpreted as a time of impaired performance. Model II was more accurate and had no underestimates for multiple doses. The most accurate approach applied a combination of Models I and II by predicting a single time interval defined by the lowest and highest 95% confidence

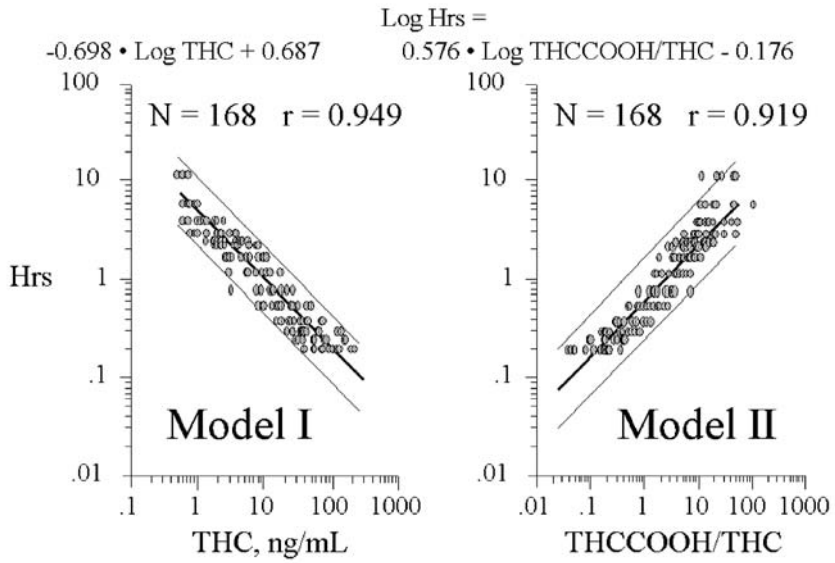

Figure 6 Two models for predicting elapsed time after last cannabis use based on single plasma delta-9-tetrahydrocannabinol (THC) concentration and 11-nor-9-carboxy-THC (THCCOOH)/THC concentration ratio.

limits of both models. For all 717 plasma specimens, 99% of predicted times of last use were within this combination interval, 0.9% were overestimated and none underestimated. For 289 plasma specimens collected after multiple doses, 97% were correct with no underestimates. All time estimates were correct for 77 plasma specimens with THC concentrations between 0.5 and 2 μg/L, a low concentration range not previously examined.

These models also appeared to be valuable when applied to the small amount of data from published studies of oral ingestion available at the time the models were developed. Additional studies were performed to determine if the predictive models could estimate last usage after multiple oral doses, a route of administration more popular with the advent of cannabis therapies. A total of eighteen subjects received oral THC as Marinol® or hemp oil containing THC [8]. Each of 12 subjects in one group received a single 10 mg oral dronabinol dose. In another protocol, six subjects received four different oral daily doses, divided into thirds and administered with meals for five consecutive days. There was a 10-day washout period between each dosing regimen. Daily doses were 0.39 mg, 0.47 mg and 14.8 mg THC in hemp oil and 7.5 mg dronabinol. Blood specimens were collected throughout the six-week study and analyzed for plasma THC and THCCOOH by GC/MS with LOQs of 0.5 and 1.0 μg/L, respectively. Actual times between ingestion of THC and blood collection spanned 0.5 to 16 h. All plasma specimens with analyte concentrations

Table 1 Predicted elapsed time between cannabis smoking and blood collection with plasma THC[a] ≥ 0.5 µg/L and THCCOOH[b] ≥ 2.5 µg/L.

	N	Accuracy (Cases within 95 % CI)	Number of Over-estimated Cases (mean time, range in minutes)	Number of Under-estimated Cases (mean time, range in minutes)
Model I				
Single dose	427	91.8 %	35 (14, < 1–41)	None
Multiple dose	290	90.3 %	25 (18, < 1–50)	3 (5, 2–11)
All cases	717	91.2 %	60 (16, < 1–50)	3 (5, 2–11)
Model II				
Single dose	415	94.0 %	4 (3, < 1–6)	21 (38, 2–94)
Multiple dose	289	97.6 %	7 (2, < 1–4)	None
All cases	704	95.5 %	11 (2, < 1–6)	21 (38, 2–94)
Combination of Model I and Model II[c]				
Single dose	415	99.5 %	2 (1, < 1–1)	None
Multiple dose	289	98.6 %	4 (2, < 1–4)	None
All cases	704	99.1 %	6 (2, < 1–4)	None

[a] delta9-tetrahydrocannabinol concentration

[b] 11-nor-9-carboxy-delta9-tetrahydrocannabinol concentration

[c] Time interval defined by the lowest and highest 95 % confidence limit of both models

> LOQ (n = 90) were evaluated. Models I and II correctly predicted time of last THC ingestion for 74.4 % and 90.0 % of plasma specimens, respectively. 96.7 % of predicted times were correct with one overestimate (0.65 h) and two underestimates (0.13 h, 0.57 h) using the combined CI.

When used in combination, the models correctly predict the time of cannabis use within a 95 % confidence interval for greater than 95 % of cases involving a single smoked cannabis cigarette, two smoked cannabis cigarettes or multiple oral doses of THC-containing preparations in less than daily cannabis users. Most controlled cannabis administration studies indicate impairment of tasks related to normal driving functions for up to 6 to 8 h after use. A small number of studies extend this time interval to 24 h for complex, multitasking operations. The predictive models provide an objective means of estimating recent cannabis use within 95 % CI that can be combined with the known pharmacodynamic effects of cannabis to develop a case of impairment. To date, there have been no controlled studies applying the models to daily cannabis users.

Daldrup et al. also developed a model employing a cannabis influence factor (CIF) that is calculated from plasma THC, 11-OH-THC and THCCOOH concentrations in μg/L and estimates impairment [73]:

$$CIF = (THC/314.5 + 11 - OH - THC/330.5)/(THCCOOH \times 0.01)/344.5$$

THC concentrations and CIF were compared to driving errors and impairment in over one hundred cases of drivers stopped at roadside in Germany [74, 75]. The authors reported that the CIF was helpful in determining impairment and, in particular, drivers with a CIF ≥ 10 were considered too impaired to drive.

Time of use and driving impairment

The effects of cannabis on driving include decreased car handling performance, increased reaction times, impaired time and distance estimation, inability to maintain headway, lateral travel, subjective sleepiness, motor incoordination and impaired ability to sustain vigilance [76]. Most behavioral and physiological effects of THC return to baseline levels within three to six hours after exposure to low and moderate doses [77–79]. Recently, Ramaekers et al. found that adults smoking high potency cannabis, i.e. THC up to 500 μg/kg, had impaired executive function as demonstrated by decreased number of correct decisions in a problem-solving task (Tower of London task) [80]. In addition, THC significantly impaired motor control and increased stop reaction time and the proportions of commission and omission errors in a choice reaction time task. THC-induced impairments were still present at the last test period that concluded 6 h after smoking. The impairment of executive function is consistent with the general observation that the greater the demands in multitasking and reasoning placed on a driver, the greater the cannabis impairment [76]. Laboratory and culpability analyses have demonstrated a dose related risk between cannabis use and automobile crashes [81, 82]. There are reports of performance impairment on some complex tasks up to 24 h after last drug exposure [83, 84].

In driving investigations, a single blood, oral fluid or urine specimen is typically collected from a driver suspected of using drugs. The plasma THC concentration (Model I) and the THCCOOH/THC ratio of concentrations (Model II) can estimate a confidence interval for the time of cannabis exposure (blood/plasma concentration ratio approximately 0.5). In fact, the most recent recommendations are to calculate the estimated time of last use with both mathematical models. The shortest and longest time from either model's confidence interval is used to develop a larger confidence interval based on both calculations. Although this approach does increase the prediction interval, the accuracy of the prediction increases considerably [7].

If the police officer observed weaving or other driving impairment and the time estimate based on laboratory findings is less than 8 h following time of use, triers-of-fact in legal proceedings have a strong basis for judging that the driver was impaired from use of cannabis. All elements of evidence are not always present and forensic toxicologists must render opinions based primarily on the laboratory results.

This requires keeping in mind the limitations of scientific studies. One caution is to ensure that the specimen was collected in the elimination phase. This is generally not a problem when opinions are based on blood or plasma results, since specimens are collected more than one hour after an incident. THC concentrations peak during smoking and the initial distribution phase for THC also is rapid (Fig. 7). The active metabolite 11-OH-THC concentration is usually less than 10% of that of THC in smokers, which minimizes its effects. If specimens are collected within one hour of the incident, it is important to know other information. THC has a counterclockwise hysteresis, meaning that the drug distributes more slowly and peak effects lag behind peak plasma concentrations (Fig. 7) [85]. Other indicators of time of use may be necessary to determine whether the driver was in the absorption or elimination phase. Effects are less during cannabinoid absorption, as seen in Figure 7.

Usually, investigators do not know the route of administration for cannabis, and drivers may claim that someone surreptitiously placed THC in their food. Peak plasma concentrations of THC occur in the 4–6 h timeframe following oral ingestion [21, 35, 39]. Also, 11-OH-THC concentrations are near those of THC and this equipotent metabolite becomes a factor in judging possible impairment. One remedy for laboratories is to measure THC and 11-OH-THC to determine if the ratio appears closer to that expected following smoking or oral ingestion. Typically, other evidence, such as police officers smelling cannabis smoke in the automobile, resolves this problem.

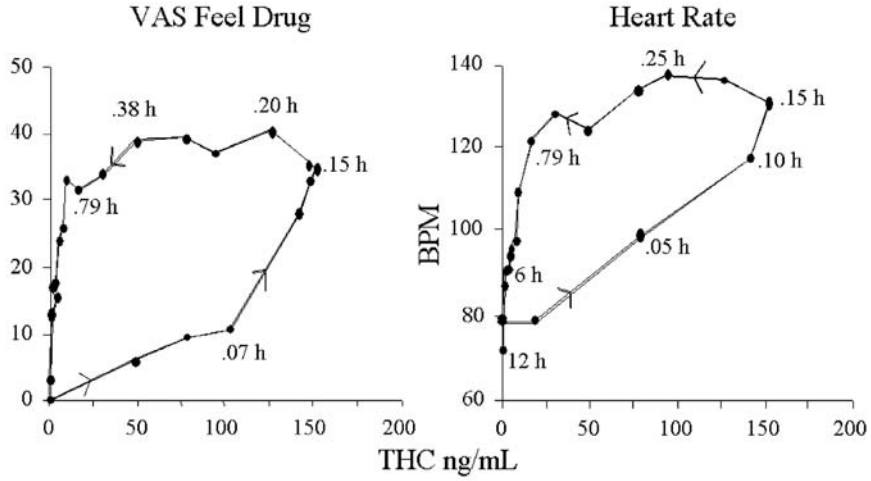

Figure 7 Changes in two effects of smoked cannabis, subjective "high" (visual analog scale rating) and heart rate, with plasma delta-9-tetrahydrocannabinol (THC) concentrations. Effects are lower during the absorption phase (prior to the end of smoking at about nine minutes) compared to the distribution phase (after the end of smoking). This concentration-effect curve displays a counterclockwise hysteresis.

An important issue in investigations is determining the frequency of drug use prior to the incident in question. As mentioned, there are limited studies on the pharmacokinetics of cannabis in frequent drug users. For example, the models by Huestis et al. have not been validated for individuals who smoke cannabis daily [6, 7]. Reports of ranges of concentrations to distinguish frequent from infrequent users have not been verified [75]. Recent studies may assist in evaluating frequent users [70]. One report indicated that frequent cannabis users performed better on some tests of impairment than infrequent users when administered the same dose [86]. More well-controlled studies examining performance and pharmacokinetics in frequent cannabis users are needed.

Cocaine

Cocaine is a potent central nervous system stimulant that blocks the reuptake of norepinephrine, dopamine and serotonin. When these neurotransmitters are released into the synapse, cocaine interacts with the dopamine transporter in the plasma membrane antagonizing the reuptake of dopamine and increases extracellular dopamine. The consequent behavioral effects relevant to driving are euphoria, excitation, dizziness, restlessness, irritability and anxiety. Physiological effects include increased heart rate, blood pressure and body temperature, dilated pupils, increased light sensitivity, nausea, and vomiting. In small to moderate doses, cocaine does not affect driving performance and in some studies improved alertness [87]. In one study of subjects impaired by alcohol, concurrent cocaine administration improved performance on laboratory tests of reaction time and memory [87]. However, more commonly cocaine users take higher doses leading to greater risk-taking and more traffic accidents [76]. Impaired driving behavior includes speeding, losing control of a vehicle, turning in front of others, inattentive driving and poor impulse control. Like other stimulants that increase extracellular dopamine, depression and lack of attention may occur after initial effects subside, usually hours after the last dose. These effects are especially pronounced after cocaine binging (repetitive consecutive doses) and may persist for several days. In this phase, accidents are more likely characterized by swerving off the roadway or falling asleep while driving [76]. Individuals who use cocaine frequently also develop tolerance. When they do not experience the expected effects from their usual dose, they increase the amount of cocaine ingested. Chronic users have been reported to administer up to 2 g of cocaine per day [88].

The route of cocaine administration impacts both its pharmacodynamics and pharmacokinetics, with the most common routes being smoking, intranasal, intravenous and subcutaneous administration [89, 90]. The advent of “crack” or cocaine base, an inexpensive and smoked drug formulation, dramatically increased the numbers and changed the demographics of cocaine users. The small, white, irregular spheres or rocks weigh 0.01 to 0.5 g, and when smoked in a pipe provide an immediate rush or high due to the rapid delivery of drug to the brain. Behavioral effects may be more intense than following intravenous administration with similar

physiological effects for equivalent blood concentrations. After insufflation (snorting) of cocaine hydrochloride, onset of behavioral and physiological effects are delayed due to the time required for the drug to be absorbed and distributed to the central nervous system (CNS), usually about 15 minutes. In addition, cocaine produces constriction of the capillaries, further slowing drug absorption. These pharmacokinetic factors result in less intense cocaine effects than following smoking or intravenous cocaine use at equivalent doses [89].

Blood concentrations of cocaine peak in about 5 min following the intravenous and smoking routes of administration. On two separate days, six subjects received the same single cocaine dose intravenously and by smoking. For both routes cocaine was eliminated rapidly with at least biphasic kinetics [89]. The alpha elimination half-lives were 0.08–0.59 h and 0.04–0.63 h, respectively. Beta elimination half-lives were longer, 1.55–9.79 h following intravenous injection and 0.75–11.37 h following smoking. The principal metabolite formed was benzoylecgonine. Benzoylecgonine appeared in venous plasma in less than 30 min. Mean t_{max} was about 2 h for both routes with mean elimination half-lives of 5.79 h (intravenous) and 5.40 h (smoking). AUC_{∞} also were similar. Ecgonine methyl ester, a metabolite present in urine, was not detected in any specimen.

In the same controlled administration study, cocaine also was given to the same six subjects by insufflation [89]. Cocaine peaked in plasma in 23 to 51 min at significantly lower concentrations than for the other routes. Alpha and beta elimination half-lives were 0.55–4.79 h and 0–11.8 h, respectively, with one subject following a one-compartment, not a two-compartment, model. Benzoylecgonine appeared in plasma within 30 min and rose gradually over 2–3 h. Ecgonine methyl ester concentrations in plasma were less than 10 μg/L.

Cocaine doses for infrequent users are approximately 50–150 mg. From controlled studies, we know that doses in this range yield peak plasma concentrations of 100–500 μg/L occurring within the first hour after use [91, 92]. Chronic cocaine abusers given free access to cigarettes containing 75 mg cocaine base maintained plasma concentrations of 250–930 μg/L over a 90 min smoking period [93]. Jufer et al. administered escalating daily oral doses of cocaine totaling 1250–2000 mg yielding mean plasma concentrations of 1260 μg/L 1–2 h after the last dose [94]. A group of 11 chronic cocaine abusers had extended mean elimination half-lives of 3.8 h; however, benzoylecgonine (6.6 h) and ecgonine methyl ester (5.5 h) half-lives were not different than those observed in occasional users [95].

Most of the studies cited measured cocaine or metabolites in plasma. Often, investigators only have blood cocaine concentrations but the studies are relevant since the blood/plasma cocaine ratio was reported to be 1.0 [96].

Cocaine is frequently consumed with alcohol, yielding an ethyl trans-esterified product, ethylcocaine (cocaethylene) [97]. Animal studies suggest that cocaine and ethanol in combination may be more cardiotoxic than either drug alone but behavioral effects are complex since ethylcocaine may attenuate the effects of cocaine [98, 99]. Elimination half-lives were reported to average 1.68 h [100].

Interpreting blood cocaine concentrations is difficult due to the large variation in effects between individuals, unknown route of administration, and possible development of tolerance. Due to these factors, cocaine concentrations cannot usually

be associated with a level of impairment, and there are no accepted models for predicting time of use. One important problem is cocaine's instability in blood, which can be mollified by ensuring that blood is collected in tubes containing an enzyme inhibiter, such as NaF (gray top blood collection tubes), and stored at 4°C or lower. Despite these protective measures, cocaine concentrations will decrease over several weeks [101].

The usual approach to interpreting cocaine blood or plasma results is to combine what we know of cocaine pharmacokinetics with other evidence. If the driver in question self-reports infrequent use and cocaine is present in the range of 200–400 μg/L, then drug exposure probably occurred within the previous 3 h. Benzoylecgonine concentrations 3 h after last use are expected to be approximately 600 μg/L following a single 106 mg intranasal dose [76, 89]. Higher blood concentrations or lower benzoylecgonine concentrations may help to narrow the range for time of use. If the driver is a chronic abuser of cocaine, interpretation is more difficult. Blood concentrations as high as 5000 μg/L are survivable in tolerant users [88].

Urinary excretion of cocaine and metabolites can be used to estimate a broader window of detection. Following single smoked 40 mg doses of cocaine, cocaine was not detectable beyond 25 h at a 10 μg/L LOQ [102]. However, after chronic administration of up to 2000 mg of cocaine, cocaine was detectable in urine (> 1 μg/L) for more than 80 h [94]. Benzoylecgonine and ecgonine methyl ester are present in urine at detectable levels for several days [102].

Amphetamines

Amphetamine and methamphetamine are CNS stimulants producing pharmacodynamic effects by increasing synaptic dopamine, serotonin and norepinephrine concentrations. Although both result in higher extracellular neurotransmitter concentrations, amphetamines' mechanism of action is different than cocaine's. Amphetamines increase the release of neurotransmitters from intracellular storage vesicles, rather than blocking neurotransmitter reuptake. As described above for cocaine, excess norepinephrine enhances alertness, anorexia, motor activity and sympathomimetic effects, dopamine stimulates locomotor effects, psychosis and perception disturbances, and serotonin is responsible for behavioral effects such as delusions and psychosis. Both amphetamine and methamphetamine are racemic with the S(+), or "d", configuration primarily responsible for effects relevant to driving impairment.

Amphetamine and methamphetamine also are effective pharmacotherapies for attention deficit hyperactivity disorder in children and young adults, narcolepsy and obesity. The United States Air Force prescribes low dose amphetamine to reduce fatigue in pilots on long flight missions. As for cocaine, low doses did not impair driving, but higher doses increased accidents primarily due to risk taking [76]. Relevant physiological effects include increased heart rate, blood pressure, respiration

rate and temperature. Heart palpitations, dry mouth, light sensitivity, irritability and tremors are common side effects. Early phase behavioral effects include euphoria (rush), excitation, rapid speech, and motor restlessness. With high or frequent doses, one also may experience hallucinations, delusions and psychosis. Effects typically last 4–8 h with residual effects up to 12 h after use.

Methamphetamine's effects are similar to those of cocaine but the onset is slower and duration of effects is extended. As for cocaine, the route of administration is an important determinant, with effects following oral ingestion much less intense than after smoking, insufflation or intravenous injection. Also, after 8–12 h following all routes of administration, users often become depressed and inattentive when driving, especially after binging.

Methamphetamine is metabolized to amphetamine, norephedrine and deaminated and hydroxylated metabolites. Following oral administration of 8.75 mg and 17 mg of deuterated d-methamphetamine mean (n = 9) peak plasma levels were 20 and 39 μg/L [103]. Mean time to peak was 2.6–3.6 h. Amphetamine peaked at approximately 12 h with mean concentrations of 1.6 and 4 μg/L. After smoked d-methamphetamine (estimated 22 mg dose) mean peak plasma concentrations were 47 μg/L at 2.5 h, with much lower mean peak amphetamine concentrations of about 4 μg/L at 12 ± 2.3 h [104]. The kinetics of oral and smoked methamphetamine are similar, unlike observations for controlled cocaine administration. Cook et al. attribute this to smokers swallowing some of the methamphetamine [104]. Elimination of methamphetamine following intravenous administration is similar to that following the oral and smoking routes. Excretion half-lives range from 6–15 h and are dependent on the pH of urine. The blood to plasma concentration ratio is about 0.65 [76].

Several authors have reported results for chronic d-methamphetamine and amphetamine administration [105–107]. Single doses up to 60 mg daily yielded serum concentrations near 100 μg d-methamphetamine/L 2 h post-dose [106]. After 20, 40, 80 and 160 mg intravenous amphetamine, serum concentrations at 1 h were 56, 124, 260, and 595 μg/L [105]. Eighteen patients administered 160 and 200 mg of intravenous amphetamine achieved plasma concentrations of 365–600 μg/L at 1 h. In another repeated dose study, subjects received four 10 mg (n = 8) or four 20 mg (n = 5) sustained-release S(+)-methamphetamine doses within a seven day period [108]. After the first oral dose, initial plasma methamphetamine detection was within 0.25–2 h; C_{max} was 14.5–33.8 μg/L (10 mg) and 26.2–44.3 μg/L (20 mg) within 2–12 h. In oral fluid, methamphetamine was detected as early as 0.08–2 h; C_{max} was 24.7–312.2 μg/L (10 mg) and 75.3–321.7 μg/L (20 mg) 2–12 h after the last dose. The median oral fluid/plasma methamphetamine concentration ratio was 2.0 across 24 h and was highly variable between subjects. Mean (SD) areas under the curve for AMP were 21 % ± 25 % and 24 % ± 11 % of those observed for methamphetamine in plasma and oral fluid, respectively. After a single low or high dose, plasma methamphetamine was > 2.5 μg/L for up to 24 h in 9 of 12 individuals (mean, 7.3 ± 5.5 μg/L at 24 h); in oral fluid the detection window was at least 24 h (mean, 18.8 ± 18.0 μg/L at 24 h). After four doses, methamphetamine was measurable for 36–72 h (mean, 58.3 ± 14.5 h) after the last dose.

In a study of 101 drivers stopped for various violations with methamphetamine as the only drug found in blood, concentrations were < 50–2360 μg/L [109]. In a recent update of impaired and fatally injured drivers, the median blood methamphetamine and amphetamine concentrations were 210 and 50 μg/L, respectively [110]. The violations listed included speeding, weaving, erratic driving, and accidents. At the stop, behaviors noted were nervousness, rapid and non-stop speech, unintelligible speech, disorientation, agitation, staggering, violence, and unconsciousness. In a separate study of 300 drivers in Sweden with only amphetamine in the blood, there was no correlation between blood concentrations and clinical effects [111]. The large range of blood concentrations complicates interpretation of laboratory results. Another problem is that both early phase, when methamphetamine and amphetamine are measurable in blood, and late phase, when these drugs have been eliminated and brain neurotransmitters are depleted, can cause impaired driving. Time of use is usually based on other information, including observed driving impairment and poor performance on the standardized field sobriety tests, as well as toxicology results [2].

Opioids

Opioids are a broad chemical class of both licit and illicit drugs including heroin, morphine, codeine, hydrocodone/hydromorphone, oxycodone/oxymorphone and methadone. These drugs interact with mu, kappa and delta opioid receptors in the brain and produce a constellation of effects. Effects are dependent on dose, route of administration and previous exposure. In general, physiological effects are analgesia, depressed respiration, decreased heart rate, nausea, vomiting, pupils fixed and constricted, diminished reflexes and drowsiness. Behavioral effects are euphoria, a feeling of well-being, sedation, lethargy and mental confusion. Effects usually occur within minutes and may last 4–6 h, depending on the route of administration, dose and specific opioid. Consequent driving effects range from no significant impairment as reported in cancer patients receiving 209 mg daily morphine [112] to slow driving, weaving, poor vehicle control, poor coordination, slow response to stimuli, delayed reaction time and falling asleep at the wheel [76].

Routes of administration for heroin include insufflation, smoking, and injection (intramuscular, intravenous or subcutaneous). Morphine is usually injected intravenously and codeine, hydrocodone, oxycodone and methadone taken orally. In recent years, the recreational abuse of oxycodone by insufflation has increased tremendously [113]. Abuse of prescription drugs is a serious health and public safety concern in the US.

An intravenous injection of 10 mg morphine/70 kg resulted in an average serum concentration at 2 min of 290 μg/L for surgical patients 23–50 years old and 490 μg/L older patients, 51–70 years old [114]. For an intramuscular injection of 8.75 mg/70 kg, serum concentrations of morphine averaged 70 μg/L at 10–20 min. Morphine is converted to O-3 and O-6 glucuronides with a serum half-life for free

morphine of about 3 h. Morphine-6-glucuronide is reported to be more physiologically active than free morphine [115] due to its rapid absorption into the brain. The inactive morphine-3-glucuronide appears in serum 20 min after intramuscular injection and exceeds morphine concentrations within 2 h [114]. In cancer patients taking 15 mg of morphine solution orally every 6 h for five days, steady-state plasma concentrations were 14 μg morphine/L, 77 μg morphine-6-glucuronide/L and 515 μg morphine-3-glucuronide/L [116].

Heroin metabolizes to 6-acetylmorphine that in turn de-acetylates to morphine. Nasal insufflation of 12 mg heroin by six adults produced mean plasma concentrations of 16 μg heroin/L at 0.08 h, 14 μg 6-acetylmorphine/L at 0.08–0.17 h, and 19 μg morphine/L at 0.08–1.5 h [9]. Mean elimination half-lives were 0.07, 0.22 and 2.8 h, respectively. In a follow-up study, additional plasma specimens from three subjects were examined for other metabolites [117]. Peak concentrations of morphine-3-glucuronide ranged from 88.2–137.4 μg/L at 1–3 h, and in one subject, morphine-6-glucuronide was 23.9 μg/L 2 h after administration. Two comparison subjects who each received 6 mg heroin intramuscularly produced peak plasma morphine-3-glucuronide concentrations of 92.9 μg/L at 0.5 h and 92.1 μg/L at 0.17 h.

In a study of smoked heroin, two subjects were administered three separate heroin doses, 2.6, 5.2 and 10.5 mg in a sealed-delivery smoking device [10]. Peak plasma concentrations of heroin were reached within 5 min and increased with dose. For the higher dose, concentrations were 108 and 229 μg heroin/L. Plasma 6-acetylmorphine concentrations were greater than 1 μg/L for 60 min in one subject and 30 min in the other. Peak concentrations were 140 and 55 μg/L at 2–5 min. Morphine was greater than 1 μg/L for 2 h in one subject and 30 min in the other with peak concentrations of 56 and 11.9 μg/L. Elimination half-lives for heroin, 6-acetylmorphine and morphine were 3.3, 5.4 and 18.8 minutes, respectively. The same two subjects received various intravenous doses of heroin for comparison. Time to peak was similar for smoking and intravenous injection, indicating rapid absorption of drug from the lungs. One subject receiving 20 mg heroin intravenously had peak plasma heroin, 6-acetylmorphine and morphine concentrations of 401, 312 and 48.6 μg/L, respectively, all within 5 min of administration. Two tolerant adults receiving 200 mg heroin intravenously had mean peak plasma concentrations of 1900 μg heroin/L at 1.3 min, 4000 μg 6-acetylmorphine/L at 1.1 min, 580 μg morphine/L at 3.8 min, 3300 μg morphine-3-glucuronide/L at 1.5 h and 1000 μg morphine-6-glucuronide/L at 1.4 h [118]. For eight subjects after single intravenous doses up to 12 mg heroin hydrochloride and 4 after 13.9 mg smoked heroin base, elimination half-lives in urine averaged (SE) 3.11 (0.30) h [119]. Peak total and free urine morphine were 1392–9250 μg/L at 1.2–6.2 h and 117–1160 μg/L at 1.2–10.1 h, respectively. Peak 6-acetylmorphine in urine ranged from 6.1–568 μg/L in the first void, the only specimen with a concentration greater than 10 μg/L.

Codeine metabolizes primarily to morphine and norcodeine. Since its central nervous system effects are approximately $1/10^{th}$ those of morphine, it can be consumed in higher doses. Typical doses are 15–60 mg with abused doses in tolerant individuals exceeding 500 mg. Time to peak is 0.5–2 h and its serum half-life is approximately 2.6 h [120]. In a study of 19 subjects receiving single codeine doses,

60 and 120 mg/70 kg, mean peak codeine concentrations (SE) were 214.2 (27.6) and 474.3 (77.0) μg/L in plasma and 638.4 (64.4) and 1599 (241.0) μg/L in oral fluid [121]. The respective mean half-lives were similar, 2.2 (0.1) h for plasma and 2.2 (0.16) h for oral fluid. Blood codeine concentrations as high as 7000 μg/L were reported in tolerant drivers [122]. Conjugated codeine in plasma was shown to exceed that of unconjugated codeine by a factor of 5.7 [123] and the blood/plasma ratio averaged 0.87 [88].

Hydrocodone is prepared from codeine with central nervous system effects similar to morphine. During metabolism it is demethylated to form hydromorphone, also a drug of abuse (Dilaudid) that is five to seven times more potent than morphine and prescribed for pain management. Serum hydrocodone concentrations vary widely but are usually in the range of 10 to 20 μg/L 1–2 h after a 5 and 10 mg dose [124]. Elimination half-lives for rapid and slow metabolizers were determined to be 4.2 h and 6.2 h, respectively [125]. The different metabolic rates do not seem to affect pharmacodynamic effects [125, 126]. Peak urine concentrations were 2500–2900 μg hydrocodone/L and 200–600 μg hydromorphone/L at 4.3–6.7 h [127]. Typical doses of hydromorphone are 1–4 mg and produce peak plasma concentrations in the range of 18–27 μg/L at 0.8–1.5 h [128]. Adult patients receiving doses every 4 h with a daily total of 48 mg hydromorphone had a steady-state plasma concentration of 20 μg hydromorphone/L and 368 μg hydromorphone-3-glucuronide/L [129]. Studies have shown that patients taking high concentrations of codeine or morphine can have, respectively, small amounts of hydrocodone or hydromorphone in their urine [130, 131].

Oxycodone is approximately equipotent to morphine with an increased prevalence of abuse in recent years with the advent of controlled-release formulations prescribed for pain management [132]. It metabolizes to oxymorphone, which is primarily eliminated in urine as O-3-glucuronides. Peak plasma concentrations following a 4.5 mg dose were 9–37 μg/L [133]. Following a 20 mg controlled-release formulation, C_{max} was 18.6 μg/L at 2.62 h and after 20 mg of immediate-release drug 41.6 μg/L at 1.30 h [134]. Oxymorphone appears in blood within 1 h but in low concentrations [135]. Peak urine concentrations after a 10 mg dose of oxycodone did not exceed 2500 μg/L [127].

Methadone is a long-acting μ–agonist used primarily for pain management and as a substitute for heroin in treatment programs. Its elimination half-life is 15–55 h [88]. Peak plasma concentrations following single doses are in the range of 30–100 μg/L 4 h after oral administration of 15 mg [136]. Tolerant subjects receiving 100–200 mg daily had peak plasma concentration between 570–1060 μg/L at 4 h declining to 460 μg/L 24 h after the last dose [136]. Methadone metabolites include 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenylpyrroline (EMDP) that are often analyzed in urine to monitor compliance [137].

Opioids can impair driving [138]. One difficulty in relating the presence of opioids in body fluids with impairment is that some dependent subjects perform better on driving tests after receiving drug [138]. Another difficulty in attempting to deter-

mine time of use by examination of body fluids is the wide concentration range for each opioid due to the rapid development of tolerance. Naïve as compared to tolerant users demonstrate different effects for similar doses and blood concentrations. Despite these complications, some helpful data are available.

Due to the rapid elimination of heroin or 6-acetylmorphine from blood, the presence of either of these compounds in blood or plasma of infrequent users indicates use of heroin within the previous 3 h timeframe. Within this time window, heroin exerts its CNS effects. The authors are not aware of any mathematical formulas for estimating time of use based on metabolite ratios, but the slower formation of conjugated metabolites provides information about time of use. The ratio of free to total morphine can be compared to literature studies and gives some estimate of time of last morphine use, provided the route of administration is known. For example, a free/morphine-3-glucuronide ratio of one would indicate intravenous injection within the previous 1 h [117]. One would expect hydromorphone to peak within 1–2 h of ingestion of hydrocodone, therefore, its absence with high concentrations of hydrocodone indicates recent use.

Oxycodone/oxymorphone ratios are not useful since the metabolite oxymorphone concentration is typically low in blood. Heiskanen et al. found a correlation between plasma drug concentrations of oxycodone following a 20 mg controlled-release dose with pupil size and Maddox-Wing neurological test scores [139]. However, they found no correlation with several other performance tests.

Conclusions

Controlled drug administration data permit scientists to develop predictive models for estimating time of cannabis use based on plasma concentrations of THC and metabolites [6–8]. From these time estimates, performance impairment, including effects on driving, can be suggested based on the known pharmacodynamic effects occurring in this time interval [2]. These models were developed for occasional users; few data are available for daily cannabis use. The small number of controlled administration studies, tolerance development, and inconsistent laboratory practices, such as application of different cutoff concentrations and analysis of different drug components in different fluids and tissues, contribute to the difficulty of interpreting drug concentrations in biological matrices [1, 140]. Some jurisdictions have developed *per se* laws establishing cutoff concentrations for toxicological analysis of biological fluids [141, 142]. Drivers detained for traffic violations with specified drugs in concentrations at or above these cutoff concentrations are presumed to be impaired. Estimating time of use remains important in jurisdictions that have not implemented *per se* laws and in providing expert witness testimony. Pharmacokinetic studies are needed to guide drug concentration interpretation, to develop predictive models for other drugs, and to guide the development of science-based drugged driving legislation.

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Remark: The opinions in this chapter are those of the authors and do not necessarily represent those of the National Institute on Drug Abuse, NIH, USA or the United States Department of Defense.

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The role of driver sleepiness in car crashes: a review of the epidemiological evidence

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Abstract

Everyday experience, knowledge about the physiology and sleep, and research under controlled conditions all suggest that driving ability is impaired by sleepiness. Epidemiological studies attempt to characterize and quantify the association between sleepiness and the risk of crashing under usual driving conditions in real populations, with the overall goal of preventing injuries. All studies are hampered to some degree by methodological challenges that arise from the multi-causal and acute nature of car crashes, and the difficulties of defining and measuring sleepiness in this context.

Despite the challenges, there is considerable evidence that sleepiness and its determinants contribute to car crashes and related injuries. Sleep deprivation, driving at time of circadian impairment, and self-identified sleepiness have been shown to increase risk. The magnitude of the risk cannot be precisely estimated due to heterogeneity in study designs, in populations studied, and in measurement of sleep-related variables. However it appears that risk increases substantially with less than 5 hours sleep in the previous 24 hours and when driving in the early hours of the morning. Some groups in the population are at particular risk, including young adults, shift workers, people with sleep disorders and people driving long distances. The road environment appears to modify the risk associated with sleepiness, with monotony exacerbating the effect. There also appears to be an important interaction of sleepiness with alcohol, even at very modest levels of drinking.

Taken together, the evidence suggests that 15–20% of car crashes may be attributable to driver sleepiness in high income countries, although there is still uncertainty about this.

Introduction

Some impairment of driving ability by sleepiness is predictable from our knowledge about both the physiology of sleep and the skills necessary to drive effectively.

This impression is supported by anecdotes and observations of drivers and their experiences.

However, quantifying the effect of driver sleepiness on car crashes, in whole populations and in specific groups is important when considering how best to intervene to reduce car crash injuries. It allows us to evaluate the magnitude of sleepiness as a cause of crashes relative to other causes, and thereby gain support for appropriate research, policy and intervention efforts. In addition to this, we also need reliable information on behaviours and conditions that contribute to driver sleepiness to provide appropriate education, regulation and other action. Finally, we need to understand differences in risk between different population groups to target measures at groups and in settings where risk is greatest.

A variety of research approaches and disciplines are being used to meet these needs. Many useful insights have been gained from studies in controlled environments, but ultimately the most important environment in which to study the relationship between sleepiness and car crash risk is on the road under "usual" driving conditions. Epidemiological studies which attempt to do this face substantial obstacles, starting with difficulties in the conceptualization and measurement of sleepiness in everyday life, and including all the methodological complexities of achieving a study design that is robust to the challenges of systematic and random errors.

This chapter briefly reviews background issues to the investigation of the role of sleepiness in causing car crashes, and then provides an overview of epidemiological studies that have approached this question.

Terminology

There is considerable variation in the way terminology of fatigue and sleepiness has been used by different authors and in different disciplines. "Fatigue" is widely used to indicate the effects of working too long, having inadequate rest, and being unable to perform tasks to usual standards [1]. It has been usefully defined as a "subjectively experienced disinclination to continue performing the task at hand" [2]. This distinguishes fatigue from the simpler concept of "sleepiness" defined as "reduced alertness as a result of increased pressure to fall asleep." [3]

The term "driver fatigue" is common in discussion of drivers and safety. In long distance driving it incorporates the duration of the driving task as a determinant of performance impairment, but this influence is much less relevant for drivers on short trips. Even amongst long distance drivers it seems that sleepiness due to sleep deprivation and circadian factors is responsible for much of driver fatigue [4], with underlying sleepiness being unmasked by prolonged monotony [5]. I have therefore used the term sleepiness in preference to fatigue as it is "identifiable, predictable and preventable"[3], and the effect of duration of driving can be measured separately. When fatigue and drowsiness have been used by other authors in the context of car driving they have been considered synonymous with sleepiness.

While the overall goal is to reduce injury, most research into driver sleepiness assesses the impact on car crashes rather than injuries. The term crash (or injury) is used in preference to "accident" in this discussion to avoid the implication of randomness.

Determinants of sleepiness

The human sleep-wake cycle is governed by both homeostatic and circadian factors. The homeostatic or "demand" component relates to an individual's prior amount of rest, where the longer the period of wakefulness the more difficult it is to resist sleep. This has been likened to hunger or thirst as a physiological need state [6]. On the other hand, circadian factors relate to one's internal body clock that produces two peaks of increased sleepiness during each 24 hour cycle. The combination of these homeostatic and circadian factors create a predictable pattern of two sleepiness peaks in each day, which commonly occur in the mid-sleep period and about 12 hours later. For most people this is about 2:00–5:00 a.m. and the middle of the afternoon [3]. In addition, sleep and wakefulness are influenced by the cycle of light and dark and so adaptation to sleeping out of phase with the light/dark cycle is not complete [7]. The sleepiness that results from the interplay of these neurobiological processes, and the diminished performance that accompanies it, occur regardless of training, occupation, education, skill level, intelligence or the commitment of the person to stay alert [1].

Effects of sleepiness on performance

Whenever people attempt to remain awake and alert during times of endogenous pressure for sleep (e.g. at night and/or after inadequate sleep) a series of predictable events occurs. Sleep propensity increases, and latency from wake to sleep and from light sleep to deep sleep decreases. More effort is required to remain awake and perform effectively, and involuntary intrusions of drowsiness and "microsleeps" increase in frequency and duration. Periods of poor, inefficient and variable performance also increase. The deficits that result include reduced vigilance with increased periods of nonresponse or delayed response (lapses), slowed information processing and poorer short term memory (cognitive deficits), and increased reaction time [1, 3].

Laboratory experiments have been able to demonstrate significant degradation of performance due to sleepiness before the occurrence of microsleeps or frank sleep onset [8], and deficits in vigilance and reaction time of a magnitude relevant to car driving have been demonstrated even in moderately sleepy persons [1]. Individuals may not always recognize the deleterious effects of sleepiness, and those who are aware of being sleepy may still not recognize that the onset of sleep is imminent [9,

10]. There appears to be variability amongst individuals in signs of sleepiness and ability to recognize them [11].

Assessment of sleepiness

There is no single tool for measuring sleepiness that is applicable to all situations. In particular, no objective measures currently exist that could be used in the immediacy of vehicle crash situations, and furthermore the crash is likely to have an effect on any such measure [3, 12]. Therefore, epidemiological studies that attempt to measure sleepiness directly, rather than behaviours or disorders associated with sleepiness, rely on self-report measures of acute (situational) and chronic (usual) sleepiness.

The Stanford Sleepiness Scale (SSS), the Karolinska Sleepiness Scale (KSS) and a Visual Analogue Scale (VAS) are all self-rating scales which have been validated to quantify progressive steps in acute sleepiness [13–16]. The most commonly employed instrument for measuring chronic or usual sleepiness by self-report is the Epworth Sleepiness Scale (ESS). While considered a validated and reliable self-report measure of daytime sleepiness, the ESS is not designed to be used as a measure of acute sleepiness or to be used in the presence of short-term conditions such as acute sleep loss [17].

These instruments have limitations. With all measures of subjective sleepiness, response may be affected by individual and contextual factors, and by the way in which the instructions are presented. Lack of understanding of the task by the subject, failure in recall, the perception of some threat in the questions, and language or cultural factors may affect response. There may also be discrepancies between subjective (or introspective) sleepiness and manifest sleepiness, observable in behaviour and performance [18].

Physiological measures of sleepiness are the gold standard against which self-report measures are validated. Measures such as the Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT) use an electroencephalogram (EEG) to determine the onset of sleep using predefined brain wave criteria under controlled conditions [18]. They are sensitive to acute as well as chronic sleepiness, but it is not possible to use these measures "in the field" for epidemiological studies of drivers.

Sleepiness in the driving population

Daytime sleepiness is a common complaint in the general population. The National Sleep Foundation's annual telephone survey of adults in the USA in 2002 (Sleep in America Poll) [19] found that 16% of the adult population were "so sleepy during the day that it interferes with their daily activities, at least a few days a week". This

was more prevalent in women (20%) than men (16%), higher in young adults than middle aged, and lowest at older ages. In 2005, this survey found 29% of American adults experience daytime sleepiness at least three days per week, and this was a little more common in women than men. It also affected more obese people (37%) than others (26%) [20]. Estimates of daytime sleepiness from other surveys vary widely depending on the wording of the questions asked, with the majority lying in the range of 5% to 15% [21]. Due to lack of uniformity in survey instruments and lack of clarity about what is considered "excessive" daytime sleepiness, it is difficult to assess the real differences between population groups [22]. However, in the 2005 Sleep in America poll, 60% of adults who drive reported they had driven while drowsy at least once in the past year, compared with 51% in both 2000 and 2002 [20]. In another sample of adults in the US, 8% reported nodding off or falling asleep while driving at least once in the past six months [23].

Epworth Sleepiness scores for daytime sleepiness have been reported for some general populations and groups of drivers. The Sleep in America poll (2000) found that 32% of the population had a scores of ≥10 (moderately affected), and 6% ≥ 15 (severely affected). It observed an association of abnormal Epworth score (≥10) with age (42% of 18–29 year olds, 30% of 30–64 year olds, 21% of those 65 years old and over); with shift work (42% in shift workers, 31% in regular day workers); and with occupational group (54% in unskilled labourers, 45% in clerical workers, 44% in service workers, 22–34% in other occupational groups). No difference was found between men and women [24]. However, amongst Australian workers, Johns found only 18% had scores ≥ 10 and 1.8% ≥ 15 [25]. Two surveys of Epworth scores in populations of drivers reported 17% ≥ 10 and 2% ≥15 in a sample of licensed drivers [26], and 26.2% ≥10 and 2.5% ≥ 15 in a sample of drivers visiting a Department of Motor Vehicles [27]. Epworth scores were also measured amongst general population car drivers used as controls in two car crash case-control studies. In Washington State, 22.5% had an ESS >10 [28] and in Auckland 9.2% had an ESS ≥10 (7.5% of men and 11.6% of women) and 1.3% >15 [29]. In a general population survey in New Zealand [30] 18.4% of drivers had a score of more than 10, supporting the observation that sleepy people probably drive less than others.

While the acute sleepiness measures described above (SSS, KSS and VAS) have all been used in laboratory situations, including simulated driving, they are difficult to use in real driving situations, as they require drivers to be stopped and tested immediately. However, drivers have been asked to recall how sleepy they were in a particular situation. For example, 0.5% of control drivers in the Washington study reported the "sensation of falling asleep on the trip"[28]. In the Auckland study, the SSS was used retrospectively by asking drivers to recall their state of alertness using this scale for the period immediately before the crash or survey, rather than at the time of questioning. Amongst the controls (who were a representative sample of the general driving population) 1% rated their level of sleepiness at 4 out of 7 (which is the statement "felt a little foggy-headed") and there were no higher scores. Just over half rated their alertness as 1 ("felt active, wide awake") and there was little difference between men and women.

Determinants of driver sleepiness

The distribution of sleepiness in the driving population is determined by the distribution of its component causes. Acute or chronic sleep deprivation, sleep fragmentation, circadian factors, alcohol and other drugs combine to determine the sleepiness of individuals and of various risk subgroups in the population.

Quantity of sleep: The degree of daytime sleepiness is directly related to the amount of nocturnal sleep. The highly consistent nature of this relationship has been demonstrated repeatedly [31]. The need for sleep varies among individuals, but seven to nine hours is required to optimise performance, with adolescents and young adults requiring more than older people. Studies of partial sleep loss suggest that functional impairment will appear rapidly with nocturnal sleep periods of five hours or less [32], and only sleep can reduce sleep debt. A range of factors can lead to sleep restriction. These include excessive hours of work, personal demands and family responsibilities, and lifestyle choices. Night shift workers are another group known to be particularly affected by inadequate sleep, and average one to four hours less than those who sleep at night [3, 7, 33].

Quality of sleep: Sleep disruption and fragmentation cause sleep debt even when sufficient hours are spent in bed. Poor quality sleep may result from any illness, and is a particular feature of sleep disorders. The most common is obstructive sleep apnoea, where a person experiences frequent brief arousals, 3–15 seconds in duration, which do not result in awakening but do result in daytime sleepiness. Similar arousals are produced by snoring, bodily pain or by auditory stimuli which are insufficient to cause the person to wake [31]. Any external cause of sleep disturbance such as noise, children, activity, lights, a restless sleeping partner, or job-related factors such as being on call will also diminish the recuperative value of sleep. Groups particularly affected by sleep fragmentation are those with sleep disorders, the elderly, parents of infants, and shift workers sleeping during the day.

Circadian factors: There is an unmodifiable biological variation in sleepiness over the 24 h cycle. The normal increase in sleepiness in the early hours of the morning and the afternoon will be accentuated by other factors such as sleep deprivation. Circadian influences are particularly problematic for night shift workers, both in reduced performance at work, and in difficulty getting sufficient good quality sleep in daytime hours. Circadian adjustment of shift workers is counteracted by a light pattern in opposition to night work hours, and so only incomplete adjustment occurs [7]. Travelers with jet lag also experience sleepiness due to the inability of the circadian system to adapt rapidly, and this is exacerbated by the sleep loss than accompanies long flights.

Monotony: People commonly use physical activity, high motivation and dietary stimulants to cope with sleep loss, masking their level of sleepiness. However, when they sit still and perform monotonous tasks, performance deficits become evident very quickly and then sleep soon follows [5, 34]. Thus, time spent driving in a dull environment without a break enables the effects of sleep deprivation to become manifest.

Sedative and stimulant drugs: Psychoactive substances are widely used, including alcohol, sedatives, hypnotics, anxiolytics, caffeine, tobacco, stimulants and

narcotics. They can be taken as prescription medications, over-the-counter drugs, recreational drugs, refreshments, and health supplements. Nearly all psychoactive substances affect the sleep-wake cycle.

In summary, it is seems clear that normal physiological processes (reflected in time of day, and time since waking) combine with a range of human conditions (e.g. insomnia, poor quality sleep) and behaviours (e.g. allowing insufficient time for sleep, taking medications, flying through time zones, shift work), and with external factors (darkness, monotony of road, time on task) to produce sleepiness in drivers, and that this is fairly common. This sleepiness diminishes driving performance and therefore the risk of a crash and injury increases.

The relationship between sleepiness and car crashes

In the 1990s several major reviews and commentaries emerged summarising evidence that sleepiness in car drivers increases the risk of crashing [1, 3, 35, 36]. An American Medical Association (AMA) report suggested that 3 % of all crashes were due to sleepiness, but other published estimates varied more than ten-fold, up to 33 % in Australia [37].These reports drew on three kinds of evidence: descriptive studies, laboratory studies and aetiological epidemiology.

Descriptive studies of sleep-related crashes include those where crashes are identified by:

- the driver having been reported by police as having fallen asleep or been sleepy;
- assuming the crash was due to sleepiness by some fixed criteria;
- self-reports from drivers involved in crashes;
- population surveys of self-reported fall-asleep or drowsy driving crashes, or by self-reported drowsy driving behaviour.

Based on these studies, the major characteristics ascribed to sleepiness-related crashes include:

- A temporal distribution that correlates with circadian patterns of sleepiness – occurring predominantly after midnight, with a smaller peak in the mid-afternoon. Young drivers are more likely to be part of the night time peak, and older drivers in the afternoon [12, 38–42];
- Serious injury is more likely than with other crashes. This is thought to be due to higher speeds, delayed reaction times and, in some cases, falling asleep at the wheel, resulting in no attempt to brake or avoid collision [12, 40, 41, 43];
- A high proportion of single vehicle run-off-the-road crashes [12, 42, 44, 45];
- More likely to be on a high speed road and/or monotonous road (e.g. motorway), and non-urban areas [1, 3, 40, 45];
- Driver alone in vehicle [42, 44];
- Drivers more likely to be young, male, more highly educated, sleep fewer hours at night, suffer from daytime sleepiness, do shift work or occupational driving, drive high annual mileage [38, 42, 46].

While generally consistent in their findings, these studies are limited in their ability to determine whether sleepiness causes car crashes and how important a cause it is. Also, since it is difficult to ascertain whether crashes are due to sleepiness or not, the crashes have often been defined in indirect ways using criteria such as "all single vehicle crashes at night with no alcohol involvement". Since sleepiness also contributes to crashes that involve other vehicles, that involve alcohol, and that occur during the day, these studies may not reflect the characteristics of all or most crashes in which sleepiness has a role.

Laboratory studies of sleep-related crashes use a proximal outcome measure such as driving simulator performance or other psychomotor test, comparing the performance of persons with sleep disorders or sleep deprivation with controls. These studies have produced some consistent findings:

- Extended wakefulness is associated with impairment in the ability to maintain lane position (tracking) and speed, increases reaction times, and increases errors of omission (lapses) and errors of commission (confusions) [47, 48].
- Total sleep deprivation and cumulative partial sleep deprivation have similar effects on simulator accident rates and divided attention tasks [48, 49].
- Performance deficits in simulated driving and unpredictable tracking tasks due to 21–24 hours of extended wakefulness are comparable to the effect of a blood alcohol concentration of approximately 80 mg–% on the same tasks [47, 50].
- Sleepiness and alcohol combine to impair driving performance more than either alone [51]), and even very low doses of alcohol potentiate the effects of sleep deprivation [52].
- Drivers can lose awareness of their ability to drive safely when they are maximally sleepy [53]. Drivers who are aware of being extremely sleepy underestimate their risk of falling asleep [54], and individuals vary in their ability to predict sleep onset [11].
- Driving performance is subject to diurnal variation in "normals" [55] and diurnal deterioration in performance is potentiated by sleep deprivation [56]. Healthy drivers can not judge this impairment well [57].
- Shift workers have a very impaired driving profile following a night of work compared with a night of sleep, but there are large individual differences [58].
- Drivers with severe untreated sleep apnoea perform more poorly on simulated driving tasks than age- and sex-matched controls, and performance improves after treatment with nasal continuous positive airway pressure (CPAP) [59].

Driving simulator studies demonstrate consistent effects of sleep deprivation and sleep disorders on performance. The fidelity of simulated driving conditions to real ones improves continually and some effects have been validated against "real world" experience, but the translation of the measured effects into risk for drivers on the road will be modified by many other contextual variables. There is some evidence from a recent cross-over study that following the same sleep restriction, reaction times are slower and sleepiness greater in driving simulators than real driving conditions [60].

Epidemiological methods

To reliably quantify a causal relationship between sleepiness and car crashes it is necessary to compare the risk of a crash in groups of drivers with and without the chosen measure of sleepiness. It is critical that the people in the two groups otherwise be as similar as possible for it to be an unbiased comparison. There are a number of generic issues that commonly affect these studies:

Selection biases: The groups being compared may not be comparable in their underlying risk of a crash, apart from differences in sleepiness. This can be due to the way they are selected or because of low response rates.

Information biases: Self-reported measures of sleepiness or outcomes such as crashes can be affected by inaccurate recall and by differences in recall between groups. Official records of crashes (and other details) are not affected by this but are usually incomplete in a non-random way [61]. Exposures and outcomes are not always measured in the same way in groups being compared.

Confounding: Crashes almost always have more than one contributing cause. Failure to adequately account for other risk factors associated with sleepiness (such as alcohol) may produce unreliable results, and they are usually overestimates of risk. If the groups differ by age, gender or the amount of driving done, this also needs to be taken into account.

Random error: studies need to be big enough to estimate risk reliably.

In addition to a clear research question, studies need to define an exposure of interest that is measurable, an outcome of interest that is measurable, and a valid comparison group. Since direct measurement of acute sleepiness is only possible by self-report, epidemiological studies have often also measured determinants of sleepiness – behaviours that result in acute sleepiness (lack of sleep, time since waking, time of day) and conditions that result in chronic sleepiness such as sleep disorders and shift work. As acute sleepiness is a transient phenomenon, a study of its effects needs a design that can measure this at the time of the crash and at a comparable time in the comparison group. The most appropriate study design for this task is a prospective case-control study [62]. In order to estimate the proportion of all car crashes that would be avoided if sleepy driving were eliminated (the attributable fraction or population attributable risk) the risk associated with sleepy driving needs to be combined with an estimate of the prevalence of sleepiness amongst drivers in the same population [63].

Epidemiological studies

The role of driver sleepiness in car crashes was the subject of a systematic review published in 2001 [64]. This review included all studies up to 2000 that had a sleepiness-related exposure measure in car drivers, a crash or crash injury outcome measure and a comparison group. This definition excluded laboratory studies and descriptive studies without a control group, and road users who potentially have

different characteristics from car drivers, such as truck drivers or motorcyclists. Exposures included measures of sleepiness at the time of the crash, measures of usual daytime sleepiness, acute sleep deprivation, chronic sleep deprivation, sleep fragmentation, shift work or other circadian rhythm disturbance, time of day, snoring and sleep disorders.

There were nineteen studies that fulfilled the review inclusion criteria, all reported between 1987 and 1999. All but one of the studies had a cross-sectional design, and an outcome measure of number of car crashes (as driver) in a specified time period. The remaining study employed a case-control design and driver injury as an outcome [65]. Most studies investigated sleep disorders (n = 14), the others were about shift work (n = 2), sleep deprivation/fragmentation (n = 1), and excessive daytime sleepiness (n = 2). Most studies were carried out in the setting of a sleep clinic (n = 11), one in hospital emergency departments, three in specific occupational groups, and four were population-based.

Overall, 13 out of 19 studies found an increase in risk of car crash or car crash injury associated with one or more measures of fatigue or sleepiness. Odds ratios for the main effect in the 19 studies ranged from 0.62 to 10.9 and, in most studies, the confidence intervals were wide. Three studies stood out because of at least moderately robust design. These all investigated sleep apnoea, but used different study designs to do so.

The first of these was the case-control study of the effect of sleep apnoea on the risk of driver injury, conducted in two emergency departments in Spain [65]. This was a well-designed study with measurement of OSA by polysomnography and questionnaire, and the cases defined by injury requiring medical attention. Major potential confounders were accounted for. The adjusted odds ratio for a crash resulting in driver injury associated with sleep apnoea was 7.2 (95 % CI 2.4–21.8), and for severe sleep apnoea was 8.1 (95 % CI 2.4–26.5). Risk was unrelated to Epworth Sleepiness Scores (mean 5.9 in cases and 5.7 in controls), and prevalence of snoring (55 % of cases and 53 % of controls), but there was a significant association between self-reported drowsiness just before the crash and the measure of sleep apnoea (apnoea-hypopnoea index).

The cross-sectional study with the best internal validity involved 295 patients who were referred to a sleep clinic in California [66]. It also used polysomnography and questionnaire and adjusted for major confounders, apart from driving exposure. It was somewhat limited by the use of non-apnoeic sleep clinic patients as the comparison group, and poor specification of the outcome events (self-reported crashes and near misses over an undefined period). The multivariable adjusted odds ratio for the association of sleep apnoea with crashes or near misses was 2.6 (95 % CI 1.1–6.3) and for the association of severe daytime sleepiness with crashes or near misses was 5.7 (95 % CI 2.4–9.2).

The third study, providing moderately strong evidence on the relationship between obstructive sleep apnoea and crashes, and also habitual snoring and crashes, used a sample of 913 state employees with driving licences from an ongoing study of the natural history of sleep disordered breathing, the Wisconsin Sleep Cohort Study [67]. Baseline data, including polysomnography, were obtained at one assessment between 1988 and 1993. Outcome data on motor vehicle crashes in the

same five year period were obtained by linkage to state records of crashes. Eligible crashes were those which involved police, involved injury, or caused > $500 property damage. Strong associations were observed in men, with odds ratios for at least one crash of 3.4 (95% CI 1.8–6.9) for habitual snorers, 4.2 (95% CI 1.6–11.3) for mild sleep apnoea and 3.4 (95% CI 1.4–8.0) for severe sleep apnoea, but no association was found in women. Self-assessed sleepiness did not explain the associations.

Overall, the review found that most studies (up to 2000) were limited in their ability to establish a causal relationship by their design, by biases, and in many cases, by small sample sizes. The better quality cross-sectional studies were suggestive of a positive relationship between fatigue and crash risk, but could not provide reliable estimates of the strength of the association. The case-control study provided moderately strong evidence for an association between sleep apnea and risk of driver injury, with an adjusted odds ratio of 7.2. This association did not appear to be mediated by excessive daytime sleepiness as measured by the Epworth Sleepiness Score (ESS). This raises the question of whether the ESS is unreliable in this context, or whether there could be another mechanism for the effect of OSA on car crash risk.

Since the time of this review a number of relevant studies have been published which improve our understanding of the role of driver sleepiness. Some main findings are summarized below.

Population-based epidemiological studies

Reports have been published of two prospective case-control studies that aimed to quantify the effect of common sleep-related exposures in the general population on the risk of a car crash. The study by Cummings et al. [28] was based in a rural county in Washington state and focused on drivers on major highways. It compared drivers in prospectively identified crashes (n = 199) with control drivers matched on driving location, travel direction, hour and day of week (n = 200). Information about a range of sleep-related exposures and a large number of potentially confounding variables was collected and analysed, including alcohol use. The main findings were a significantly increased risk of a crash for drivers who felt they were falling asleep on the trip (RR = 14.2; 95% CI 1.4–147), those who drove longer distances (RR = 2.2 for each additional 100 miles; 95% CI 1.4–3.3) and those who had slept nine or fewer hours in the previous 48 hours.

The second study [68] was conducted in the Auckland region of New Zealand, including both urban and rural driving. It studied all drivers involved in crashes in which one of the car occupants was hospitalized or killed, identified prospectively from the region's trauma hospitals (n = 571). They were compared with unmatched control drivers sampled from the roads in the region using random stopping sites on the same range of road types as the cases (n = 588). Information was collected on many potential confounders, including alcohol use. This study found a significantly increased risk of an injury crash for drivers with a Stanford Sleepiness Score of

4–7(sleepy) *vs*. 1–3 (alert or relaxed) (RR = 8.2; 95 % CI 3.4–19.7). It also calculated the risk associated with five or less hours sleep in the last 24 hours (RR = 2.7; 95 % CI 1.4–5.4) and driving between 2:00 and 5:00 A.M. compared with other times of day (RR = 5.6; 95 % CI 1.4–22.7) after adjusting for alcohol and other confounders. Since the controls were a random sample, the population attributable risk for driving with one or more of these acute sleepiness risk factors could be calculated and was shown to be 19 % (95 % CI 15–25 %).

As can be judged from the wide confidence intervals, both of these studies would have benefited from being larger, but their results for acute sleepiness are not incompatible. The findings related to chronic sleepiness were also fairly similar. There was a suggestion of an increase in risk associated with a history of OSA in the Washington study and with a triad of OSA symptoms in the Auckland study, but neither finding was statistically significant, reflecting how much less common sleep disorders are than other causes of sleepiness in a general population. Neither study found risk to be associated with Epworth Sleepiness Scores, consistent with the findings in the previous case-control study of sleep apnoea and injury risk [65] and the Wisconsin OSA study [67]. Taken together, these two case-control studies suggest that when drivers themselves are aware of sleepiness they are at increased risk and, even allowing for some possible recall bias, the risk seems substantial. It also appears that the threshold for sleep required to avoid an increase in risk is around five hours a day, as predicted by experimental data. These findings, along with the increase in risk from driving between 2:00–5 A.M. provide useful messages for education of the public.

The finding that self-reported sleepiness while driving is associated with higher crash risk has been reproduced in a large French cohort study [69] where there was no recall bias since the frequency of sleepiness while driving was measured before the crashes occurred. This study found that the risk of a serious crash over a three year follow up period was increased by 1.5 times in those who reported driving while sleepy a few times a year, and three-fold in drivers who experienced sleepiness while driving once a month or more. When drivers with a sleep disorder were excluded from the analysis, the risk associated with sleepiness once a month or more increased to almost five times the risk of a never-sleepy driver.

Situations of high risk

Holiday driving

Long-distance holiday drivers have been shown to have a higher level of sleep deprivation and other measures of sleepiness. From the study of large groups of car drivers in France, Philip has demonstrated that long-distance driving is very frequently associated with sleep curtailment beforehand [70]. In a sample of more than 2000 drivers recruited at freeway tollbooths, of whom 81 % were holiday makers, 50 % of drivers had reduced their total sleep time in the 24 hours before their

departure on a long distance trip. As a result, 12.5% had a sleep debt of more than three hours and 2.7% had a sleep debt of more than five hours. Overall, 10% had fewer than five hours of sleep in the previous 24 hours, when mean usual sleep was 8.5 hours. Fifteen percent were on the road in the most dangerous period for sleepiness, between 2:00 and 6:00 A.M.

Obstructive sleep apnea (OSA)

There have been several further studies published that support a role for undiagnosed OSA as a contributor to car crashes. However, due to the lack of prospective studies, uncertainty about the size of the effect remains. One recent review [71] suggests that the crash rate for OSA sufferers is 2–4 times that of the population at large. The evidence that the relationship is not mediated by excessive daytime sleepiness (as measured by ESS) raises both a scientific question about the mechanism of effect and an additional safety concern. If drivers with OSA do not experience excessive sleepiness they are unlikely to take extra precautions when driving [72].

Shift work

A sizeable minority of the working population in high income countries work shifts. Circadian influences are particularly problematic for shift workers, both in reduced performance at work and difficulty in getting sufficient good quality sleep in daytime hours. The resulting cumulative sleep debt compounds sleepiness during work periods and when commuting to and from work, and affects levels of sleepiness on days off work. Some attention has been focused recently on the risk of car crashes associated with junior doctors' conditions of work, both the duration of shifts and night work. A prospective cohort study of interns in the USA found that residents who had worked 24 hours or longer were 2.3 times more likely to have a motor vehicle crash following that shift than when they worked less than 24 hours and that the monthly risk of a crash increased 16% for each additional extended shift [73]. A large cross-sectional survey of emergency medicine residents found that three-quarters of reported car crashes occurred following night shift, and that the risk of a crash was significantly associated with the number of night shifts worked per month [74].

Road environment

Monotonous driving environments have long been identified as increasing the risk of sleep-related crashes due to the unmasking effect on underlying sleepiness. A recent audit of traffic crashes in the UK [75] identified 17% of crashes as being sleep-related, but that this proportion varied from 3 to 30% depending on the road type.

The report found that higher traffic density was associated with a higher number of sleep related crashes in city driving but was protective on highways. Artificial lighting on motorways during hours of darkness decreased sleep-related crashes a little, but naturally longer daylight in the summer did not. The study also identified points where clusters of sleep related crashes occurred, presumable due to road design features.

Sleepiness and alcohol

Alcohol, as a CNS depressant, acts to increase sleepiness but it also independently produces some psychomotor and cognitive impairments that are similar to sleepiness. In combination, this results in producing performance impairment greater than adding the two together. It is likely that this is most important at low levels of blood alcohol, where alcohol alone may not increase crash risk by very much and people believe themselves to be safe drivers.

Alcohol use in the presence of sleepiness has been shown to have a dramatic effect on driving ability in both simulator studies and a few epidemiological studies. For example, a study conducted using a motorway simulator has demonstrated the effect of combining sleep restriction (to five hours) and a blood alcohol concentration (BAC) of 30–40 mg–% [76] in young men. At 30–60 minutes into the two hour drive the combined effect on lane drifting was greater than the sum of the detrimental effects of the two conditions separately. Interestingly, the male drivers did not subjectively experience additional sleepiness due to the alcohol over and above the affect of sleep restriction alone, although it was evident on EEG. When the study was repeated in women [77], they did not seem to be impaired by the low levels of alcohol except when sleep-deprived as well, and they were aware of the enhanced sleepiness due to combining alcohol with sleep restriction. In a similar study in the USA, women predicted crash risk when sleepy more accurately than men but this difference was abolished by low levels of alcohol [78]. It seems that even the combination of modest sleep debt, the afternoon circadian dip and a drink at lunchtime could produce substantial and unsuspected impairment of driving, let alone driving home tired at night after a party.

Unfortunately, most population based datasets from research about driver sleepiness and crashes do not have reliable alcohol measures, and most drink driving studies have inadequate measures of sleepiness to separate the effects of the two. The situation is further complicated by the prevalence of drink driving having a similar distribution to circadian patterns of sleepiness, being maximal in the early hours of the morning.

One population based study has explored this interaction using sleep and time-of-day data from the Auckland case-control study. Driver sleepiness scores were derived from the participant data and the interaction of sleepiness and alcohol in determining crash risk was analysed [79]. In addition to an increase in risk of 1.5 times for each step on the nine-step sleepiness scale for drivers with zero BAC, it found that this increase was more than doubled for drivers with a BAC of 3–50 mg% and

tripled with BAC > 50 mg%. It appeared that some of the increase in crash risk attributed to low levels of alcohol may be due to sleepiness in these drivers. However, due to the modest size of this study further research is warranted in this area.

Conclusion

There is considerable evidence that sleepiness, and the impairments accompanying inadequate sleep, contribute to causation of car crashes and resulting injury.

Epidemiological studies are limited by a range of methodological challenges that hamper all studies of traffic injury, such as having to deal with multiple contributing causes, but also by sleepiness being intrinsically difficult to define and measure in this context.

For these reasons, and because effects seem to vary greatly by individual and by context, the magnitude of risk associated with "sleepiness" cannot be precisely estimated. However, sleep deprivation, (whether cumulative sleep debt or acute lack of sleep), driving at times of circadian impairment, and self-identified sleepiness have been shown to increase car crash risk. Some groups of people experience these conditions more than others, including young adults, shift workers, people with sleep disorders, and people setting out on long holiday drives. Monotonous driving environments exacerbate the effects of sleepiness, and some features of the road environment may be protective. The combination of sleepiness with alcohol, even at very low levels, substantially heighten risk. It seems likely that between 15 and 20% of car crashes are due to driver sleepiness in high income countries. However, there is considerable uncertainty about this.

Much of the burden of injury due to sleepy driving occurs in "normal" people. However, characterization of risk in the general population has proved difficult, and motivation to pursue this is tempered by the lack of population-based interventions that might be effective in reducing the burden. Even drivers who recognize sleepiness while driving seem to underestimate its impact on risk, or overestimate their ability to overcome it, and continue to drive. Others seem unaware of their impairment. Some research is focusing on interventions in high risk activities such as holiday driving and shift work or on people affected by sleep disorders, and this is warranted because of higher risk in these groups of individuals. However, at a population level it is much more difficult to see how best to intervene. Public health education campaigns without accompanying regulatory or environmental interventions have a poor record of efficacy.

In some countries it may be possible to provide a stimulus to change public attitudes about sleepy driving through enhanced employer responsibility for commuting safety, and restrictions on driving at high risk times. While protecting employees, these moves also identify driver sleepiness as an important safety concern and may influence behaviour in the general population. Also, given the important interaction with low levels of alcohol, sleep related crashes may be able to be reduced by stricter control of alcohol use by drivers.

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Sleepiness, countermeasures and the risk of motor vehicle accidents

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Abstract

There are several factors that increase the risk of driver sleepiness and result in increased accident risk. Modern vehicle design enables the driver to travel at high speeds and for long distances in a comfortable and often sleep promoting driving environment. Recent decades have seen an increase in shift work and apparent trends for reduced sleep length, which combine to increase driving risk, particularly with night driving. The young appear more vulnerable to the effects of reduced sleep, night driving and driving for long periods. Sleep related vehicle accidents represent a high proportion of vehicle accidents with the young and truck drivers standing out as vulnerable groups. People appear to be relatively poor predictors of imminent sleep onset so that driver warning systems would provide a valuable countermeasure, but unfortunately reliable commercial systems are still some years away. Future warning systems will need to account for the marked individual differences seen in levels of driver sleepiness, impaired performance and associated risk levels. Driver education programmes are required warning of the increased risks of driver sleepiness associated with extended waking, too little sleep, and driving during the circadian low period. Drivers should also be made aware of strategies helping to maximise sleep and optimise arousal which are of particular use for night driving and shift work. These could include the use of appropriate hypnotics to maximise available sleep, or melatonin and light exposure to enhance phase shifting or improve sleep and waking scheduling. Practical countermeasures used by drivers that have been assessed and appear beneficial include the use of brief naps and caffeine.

Introduction

Improvements in design and technology have contributed to a reduction in motor vehicle accidents across the UK in recent decades, although the role of the driver in driving accidents remains. Twenty years ago, John Lauber from the US National Transportation Safety Board delivered the keynote address to the second annual

meeting of the Association of Professional Sleep Societies on sleepiness, fatigue, and circadian factors in transport accidents, reporting nearly 48 000 deaths and an associated cost of over 50 billion dollars from total highway accidents in 1986 [1]. Perhaps these figures, together with the landmark paper of Damien Leger that provided a similar cost estimate for total US sleep related accidents in 1988, has helped focus attention and research on sleepiness and driving [2]. This chapter outlines some of the key variables that affect driver sleepiness and have relevance to drugs, driving and traffic safety.

The development of motor vehicles over the last century has seen remarkable changes in design and performance. Count Gaston de Chasseloup-Laubat achieved nearly 40 mph in 1898, with Louis Rigolly breaking the 100 mph barrier in 1904 and Andy Green achieving over 760 mph in 1997 [3]. Today, many production cars can easily exceed 100 mph and go much further without stopping than a human can travel on foot. Combine this performance with an interior environment that can match a modern home for equipment, comfort and climate control, add in long monotonous journeys that can be made at any time of day or night, and it is not difficult to see why driver sleepiness remains a key factor in accident figures [4].

Perhaps the first question to ask is why should we feel sleepy? Part of the answer can be found through studying the need for sleep. The search for the functions of sleep continues although there is increasing awareness of the importance of sleep for the maintenance of normal mind and body functions, including peaks in growth hormone release accompanying slow wave sleep to assist cell growth and repair [5]. Newer theories emphasise the role of sleep in maintaining brain function including synaptic homeostasis and the role of REM sleep in memory consolidation [6, 7]. The functions of sleep at a cellular level are now beginning to be understood, including differential switching of gene activation for both sleep and waking functions [8]. Whilst prolonged periods of waking have been achieved voluntarily, such as the 11 day marathon of Randy Gardiner, sleep researchers believe sleep is essential for survival [9, 10].

Given the importance of sleep, and the fact that the population spends around a third of their lives sleeping, it is not surprising that there is a strong drive for sleep and that sleep can occur across the 24 hour day and night cycle, sometimes coming at inappropriate times [11]. Indeed, this irresistible drive for sleep is assessed in the "maintenance of wakefulness test" where participants are asked to try and remain awake whilst in bed in a sleep promoting environment [12, 13]. The relative ease with which we can fall asleep during the day is measured in the "multiple sleep latency test" finding norms of around 10 minutes, although young adults may achieve sleep in half this time, suggesting they may be chronically sleep deprived but perhaps also reflecting the strength and integrity of their sleep drive [14, 15].

The evolutionary survival of sleep amongst mammalian species and the irresistible urge to sleep experienced by nearly all humans comes at a cost when modern living has freed us from the natural zeitgebers of light and dark, enabling waking activity at any point across the 24 hour cycle [16, 17]. Driver sleepiness and sleep related accidents may be seen as a consequence of pushing human endeavour beyond our physiological capabilities that have evolved over the millennia. This

overview begins by looking at the effects on driver sleepiness of extending waking, reducing sleep and moving the phase of our sleep and wake activity across the 24 hour light/dark cycle.

Extended waking, sleep restriction and circadian rhythms

Human error is a major component of transport and other accidents. Key components of driver sleepiness are the effects of extended waking or sleep deprivation where the driver has been without their normal sleep. Prolonged periods of driving or other work result in fatigue and are frequently compounded by trying to continue working at a time when we would otherwise be asleep, usually during the night. These two influences can combine to produce marked decrements in driving and performance in general.

At the same time as the first motor cars were being made, Patrick and Gilbert were undertaking the first published studies on sleep deprivation, observing mental lapses and performance decrements in their participants after the first night of sleep loss [18]. There has been considerable research into the effects of extended waking and sleep deprivation and the last 50 years have seen a marked increase in research and knowledge. Early findings included the discovery of "blocks" in mental performance that increased in frequency and duration with increasing fatigue [19, 20, 21]. The "Walter Reed lapse hypothesis" developed from studies noting that whilst the fastest reaction times remained relatively stable with over 60 hours of sleep loss, there was a marked increase in the slowest responses suggesting lapses or gaps in performance [22]. The use of the electroencephalogram (EEG) has demonstrated brief "microsleeps" that can be coincident with performance lapses, and this measurement approach has been useful in developing measures of sleep detection [23]. Clearly, driving requires continuous attention and even brief lapses at modern driving speeds can have severe consequences.

Whilst it should be common sense that sleepiness and poorer driving increase after no sleep at all (total sleep deprivation), the potential for driving impairment after restricted sleep (or partial sleep deprivation) may not be so obvious. Early studies suggested that regular nightly sleep duration could be reduced although there was a "titration point" at about 4.5 hours below which sleep could not be reduced without marked increases in daytime sleepiness and deterioration in performance [24]. More recently smaller reductions have been shown to affect subsequent waking, but equally striking has been the discovery that reducing sleep to around four hours a night can produce as marked effects as a night of total sleep deprivation. Chronic sleep restriction of four or six hours a night produces both dose-response and cumulative deterioration in performance across nights [25, 26]. These findings are of relevance as there has been much debate about whether modern living is associated with a state of chronic sleep loss [14], with 16% reporting sleeping less than six hours on weekday nights, representing a 4% increase between the 1998 and 2005 Sleep in America polls [10].

From birth onward there is a period of entrainment such that the newborn baby begins to "fit in" with the external world of their parents or caregivers, gradually sleeping more at night and being more active during the day [27]. Once established, this endogenous circadian rhythm is slow to change and even daylight saving time enforcing a one-hour phase advance in spring can be disruptive [28].

Endogenous rhythms or changes in activity appear to be a fundamental property of living organisms, with the Dutch astronomer de Mairan (1724) being amongst the first to report rhythms that may be independent of environmental changes when he observed patterns of leaf movement [29]. The suprachiasmatic nucleus (SCN) of the mammalian brain has been established as the centre for the genetically based circadian clock or pacemaker, although interconnections with other regions mediate responses to food and social interaction as well as physical environmental changes, including light and temperature [30, 31]. The interaction of the SCN with other brain regions appears to govern our sleep and waking activity patterns and consequently our levels of alertness [32]. Different models have been proposed to account for increasing sleepiness with extended waking and underlying circadian variation. These include the homeostatic sleep drive that increases with waking duration until sleep occurs, and the background circadian system accounting for variation in waking levels of alertness [33, 34, 35].

Variations in performance across the day have also long been recognised, with Ebbinghaus (1885) reporting variations in the rate of learning and a "sleepiness rhythm" proposed by Gates in 1916 [36]. The link between body temperature and performance was reported by Nathaniel Kleitman in 1939 in his classic book "Sleep and Wakefulness" [37]. The low point of the body temperature rhythm coincides with the normal sleep period for a diurnally adjusted human and this trough coincides with the sleep related accident peak for young drivers in the early morning hours. Similarly, the "post lunch dip" described by Kraepelin (1893) is associated with an accident peak in older male drivers [36, 38].

These three key factors of extended waking, restricted sleep and circadian rhythms are explored in more detail with specific reference to driver sleepiness and accidents.

Most of us are adapted to sleeping at night and being active during the day, so that shift work requires employees to change their sleep/wake schedules, working when their physiological rhythms are in a sleep phase and conversely attempting to sleep when their underlying circadian rhythms are in an active phase. When shift workers attempt to sleep during the day their sleep is of shorter duration and more disrupted with increased waking. This in turn is associated with poorer performance at night, including slower responses and higher error rates, reflecting both the consequences of disturbed sleep and working during the circadian low period, and consequently a recovery period is required after a period of night shifts [39, 40, 41]. Night shift working is associated with increased sleepiness, with 50 % of both train drivers and controllers reporting severe subjective sleepiness representing a six fold increase compared to the day shift; the risk increasing by 15 % for each hour of the shift and decreasing by 15 % for each hour of sleep obtained, emphasising the link between shift work sleepiness and prior sleep [42]. A comparison of

high, medium and low fatigue calculated from work history found that train drivers in the high fatigue group were using more fuel and involved in more heavy breaking and speeding violations, affecting safety [43].

Extending waking may be a normal consequence of shift work, for example when moving from day to evening shifts in a rotating shift system. A controlled laboratory study found that lapses in behavioural alertness were approximately linearly related to extended waking of more than 16 hours and may partially reflect the above increase in severe sleepiness with hours worked for train drivers [26]. These findings can be compared to those of Rosa, who found a three-fold increase in accident rates after 16 hours of working, suggesting caution in extending work shifts [44].

Studies that assess the effects of repeated nights of restricted sleep are also of relevance to shift work. More than a decade ago Gillberg pointed out that even a two hour reduction in normal sleep length had a negative effect on alertness. More recently a comparison of four, six and eight hour sleep durations has shown a dose-response deficit in performance, although subjective sleepiness did not distinguish the two levels of sleep restriction. Chronic sleep restriction (14 nights) to six hours or less was equated with two nights of total sleep deprivation, showing that even moderate sleep restriction can impair waking function [26, 39]. Further research has shown that even minimal chronic sleep restriction to seven hours is associated with significant decrements in waking performance [10]. These laboratory studies clearly show the adverse impact of repeated nights of sleep restriction and support the above findings for train drivers. They are a cause for concern when compared to findings from surveys (see Connor's chapter elsewhere in this book), where an earlier study has shown over 20% of drivers reported only up to four full nights of sleep in the past week and 3% reported sleeping up to five hours [45].

The significant increase in shift work in recent decades has itself increased night driving either as part of work activity or in travelling to and from work. A roadside survey conducted in New Zealand found 8% of drivers were shift workers [45]. Irregular shifts combined with potential environmental stressors of heat, noise and vibration as well as heavy physical work for lorry drivers, are all implicated to increase fatigue and sleepiness [46]. Gillberg and colleagues reported slower night driving, increased sleepiness, speed and lane variation for professional truck drivers in a simulator study comparing night and day driving [47]. Furthermore, driving home simulation after a night shift resulted in an increased number of incidents (drifting outside of lane markings), increased variation in lateral position (e.g. lane drifting) and reduced time to first "accident" when compared to a normal night sleep [42].

The author experienced a decade of night shift work as a sleep researcher and was well acquainted with the difficulties in sleeping during the day, staying awake at night, driving home, and the marked fatigue and sleepiness associated with prolonged shifts.

Increased health problems are also associated with shift working, and shift work sleep disorder occurs in about 10% of shift workers [48, 49]. Not all people react the same way and some appear more tolerant to shift work than others. Individual

differences have been found in both subjective sleepiness and driving performance. Harma proposed that a variety of factors affected sleepiness in shift workers, including social factors, domestic situation, personality and coping strategies as well as age, sex and physical fitness but concluded that they predicted only a minor part of the differences in sleepiness between individuals [50].

A comparison of simulated driving performance found marked individual differences in driving (lateral position) and subjective sleepiness after a night shift compared with a normal nights sleep [51]. Galliaud and coworkers studied participants who were "resistant" and "vulnerable" to sleep loss and found the resistant group showed less deterioration in response times across the night when compared to the vulnerable group, although changes in subjective sleepiness were less marked and brain activity (EEG) changes were similar for both groups [52]. Whilst there is variability in response between people, individual participants show a stable response pattern reflecting a trait characteristic and possibly genetic determinants [10]. Young drivers showed a greater slowing of reaction time when they had driven more than eight hours compared to older drivers [53]. Age differences were found for early morning (3:00–6:00 am *versus* 10:00–12:00 am) road accidents where drivers were either seriously injured or killed, indicating a five-fold increase in accident risk for the young compared to a reduced risk for older drivers, and that men represented a two-fold risk compared to women for night driving [54]. This increased vulnerability for young drivers has been borne out in a controlled laboratory study of response time where young participants showed significant increases when tested across a night of sleep deprivation reflecting performance decrements, whilst older participants response times remained more stable. Subjective estimates of sleepiness and performance were equally affected between young and old, suggesting an age dependent difference in perception [55]. These studies demonstrate that both group differences (age, gender) as well as other individual differences exist in susceptibility to the effects of extended waking and circadian desynchronisation.

Overall, these findings show that night work is associated with greater sleepiness and deterioration in performance. This may be linked to poorer sleep during the day and circadian disruption. Driving simulator studies and analysis of road accidents figures have indicated poorer night driving and impairment in driving home after a shift. However, there are individual differences, including age and gender, in response to night working and driving performance which affect accident risk.

The increase in subjective sleepiness during the night and impairment in driving performance are illustrated in Figures 1 and 2, taken from our own studies [56]. The study compared subjective alertness and driving simulator performance at midday and 10 pm baselines compared to daytime alcohol (0.1 %) blood alcohol concentration (BAC); above UK legal driving limit) and night driving at midnight, 2:00 am and 4:00 am. Subjective alertness is decreased after alcohol, but shows a greater and progressive decline from midnight to 4:00 am reflecting an increase in sleepiness. A progressive deterioration is also apparent in driving performance with the number of off-road events (driving over the road boundary) increasing from midnight to 4:00 am, with the 4:00 am performance being significantly worse than driving after alcohol consumption. The midnight test point would equate to approximately 16

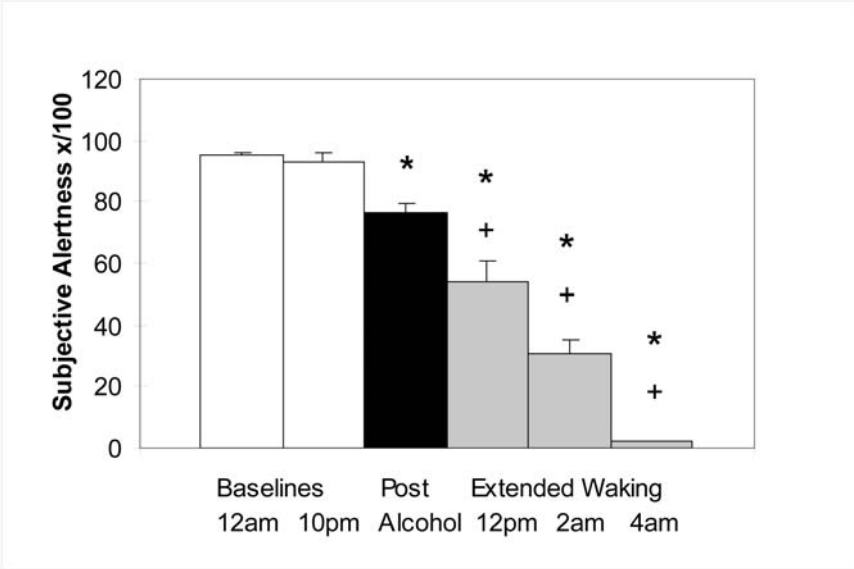

Figure 1 Subjective alertness during the day and across the night compared to daytime alcohol 0.1 % BAC; (means, SEM, N = 12) higher scores represent being more alert. * P < 0.05 *vs*. baseline; + P < 0.05 *vs*. alcohol.

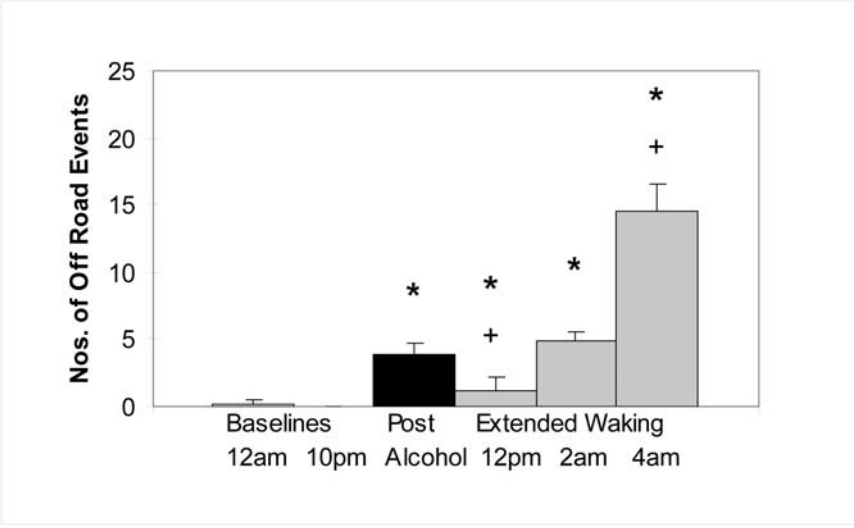

Figure 2 Number of "off road events" on driving simulator during the day and across the night compared to daytime alcohol 0.1 % BAC; (means, SEM, N = 12) higher scores represent poorer driving. * P < 0.05 *vs*. baseline; + P < 0.05 *vs*. alcohol.

hours of waking, so that our laboratory findings support the above literature showing deterioration in performance after 16 hours of waking or work.

The relative importance of driver sleepiness in road accidents

Human error is the primary cause of accidents, and modern increases in 24 h operations result in increased sleep and fatigue related accidents [57]. Impaired or reduced sleep is a major cause of transport accidents, and this is often associated with the driver undertaking night and early morning work whilst being at a circadian low, resulting in a higher overall risk for night driving [54, 58]. Whilst the previous section has focused on the impact of sleep loss, extended waking and circadian rhythm disruption on driving, the overall impact of sleepiness on driving accidents is considered here.

Early studies identified the relative importance of sleepiness as a factor in serious or fatal accidents. Twenty years ago Parsons examined causes of loss of consciousness whilst driving and found that drivers who fell asleep represented only 27% of his sample but accounted for 83% of deaths, showing the severe consequences of falling asleep at the wheel [59]. Maycock reported that around 10% of car accidents were associated with tiredness in the UK, whilst Bonnet and Arand found fatigue was a factor in 57% of truck driver and 10% of car driver fatalities in the US [14, 60]. More recently 10–15% of fatal accidents were attributed to sleep and fatigue in Finland [61]. Sleepiness may be a particular hazard for truck drivers, where a high proportion of accidents have been attributed to fatigue (52%; 31% fatal accidents) although only 18% of drivers admitted falling asleep [58].

A wider range of figures for sleep related accidents has been given in some later publications, with differences attributed to the methods employed and the possible consequences of admitting sleepiness amongst those surveyed [12, 58, 61, 62]. A figure of around 20% for sleep related driving accidents has been reported in several recent publications, which clearly emphasises the importance of driver sleepiness as a major factor [4, 12, 63]. A detailed analysis of the epidemiological evidence is provided by Connor elsewhere in this book.

Given the high proportion of sleep related accidents, a logical question is whether there are any associated signs or predictors. Maycock found that 29% of car drivers reported they had been close to falling asleep within the previous 12 months, whilst 20% of long haul truck drivers reported dozing off at least twice in the preceding three months in a Finnish study and 17% of those reported near misses as a consequence [60, 64]. Sleepiness has been proposed as contributing to 24% of crashes and near misses representing a four- to six-fold increase in risk in the US, with an eight-fold increase in accident risk associated with acute sleepiness in a New Zealand Survey [8, 62]. A large survey in the US has shown that sleepy-driver near misses can predict accident risk. A dose response relationship was shown with the accident risk doubling for drivers with a history of at least four near misses due to sleepiness [65].

The New Zealand survey of drivers involved in serious or fatal accidents also identified sleeping no more than five out of the last 24 hours as representing a nearly three-fold increased risk, and approaching six-fold for driving between 2:00 and 5:00 am supporting the earlier findings of Horne and Reyner for younger drivers [38, 62]. Similarly, the five-fold increased risk reported in a Swedish study for young night drivers may reflect Bonnet and Arand's earlier warnings of acute sleepiness in the young as a result of taking insufficient sleep [14, 54]. A study assessing driver response speed (reaction time) at a rest stop found that slow responses were predicted by the duration of driving and the shortness of breaks taken. Young drivers were particularly susceptible to slowed responses after eight or more hours driving [53].

These findings show that driver sleepiness results in a marked increase in relative accident risk, and that sleep related accidents may represent around 20 % of total driving accidents, but more for vulnerable groups such as the young or professional truck drivers. Accident near misses provide a predictor for sleep related accidents. The association of acute sleepiness and near misses with increased accident risk leads on to the question of whether drivers can themselves predict that they are about to fall asleep.

A common sense approach would suggest not, as no one has suggested that drivers knew of the impending consequences in the high proportion of serious or fatal sleep related accidents. It has been suggested that drivers will know when they are sleepy and should therefore stop driving [38]. However, a recent laboratory study assessed the ability of participants to predict whether or not they would fall asleep in the next two minutes. Only 55 % were correct in predicting first sleep onset. Poor predictors were found either not to acknowledge signs of impending sleep, including eye closure, head nodding or wandering thoughts, or that these predictors were scarce [63].

The realisation that sleep related driving accidents are a major concern has led to research to establish accurate measures of impending sleep that may be used to monitor drivers, and to developing potential countermeasures that may prevent sleep related accidents.

Measuring sleepiness

If sleepiness is defined as subjective feelings of being sleepy and the increased or imminent likelihood of falling asleep then there are both subjective (feeling sleepy) and objective (physiologically or behaviourally falling asleep) assessments involved. Performance measures should also be included, as this chapter is concerned with sleepiness and the risk of motor vehicle accidents (impaired driving performance resulting in an accident). The consistency and agreement between these three types of measure are important for both studying driver sleepiness and in trying to develop effective warning systems for transport operations. Some ex-

ample measures are outlined in this section before considering approaches used in the development of vehicle warning systems.

Physiological measures

A variety of other physiological measures have been investigated as potential measures of sleepiness for driver monitoring, including heart rate and biochemical sensors, but the emphasis has been on the use of EEG as a measure of cortical arousal [46].

EEG

Richard Caton, who went on to become mayor of Liverpool, is believed to have been the first person to record the electrical activity of the brain, stating in his second publication (1877) that "a variation in the current frequently occurred when the rabbit awoke from sleep"[66]. Changes in brainwave or EEG activity have provided an objective measure to assess changes from sleep to waking that can be useful in assessing sleepiness. The "R&K" standardisation of sleep scoring classified sleep into five stages (NREM 1–4 and REM), with waking as a single stage [67]. No standardised system for classifying levels or stages of waking has been agreed on, although attempts have been made. We developed a polysomnography based system which was continuous with R&K sleep, separating waking into six levels from "active" to intermittent theta or "microsleeps" [68].

Earlier attempts to assess sleep onset have included the work of Ogilvie and Wilkinson comparing a behavioural response, pressing a switch in response to a faint auditory tone, to EEG and subjective parameters. They found that responses were possible during stages 1 and 2 sleep [69, 70]. The author has also witnessed responses from stage 2 sleep when showing a guest the sleep lab and indicating from the EEG that the participant was asleep – only to receive a muffled contradiction through the wall indicating they were awake! Clearly, even the widely used EEG does not provide a definitive marker for "sleep onset" or lack of behavioural response, which is the key point for assessing sleepiness in drivers. None the less, Lal and Craig considered the EEG as "perhaps the most promising of psychophysiological indicators" in their review of driver fatigue [46]. As mentioned, earlier research had suggested that "microsleeps" were consistent with "lapses" in performance, researchers went on to find changes in EEG consistent with a loss of vigilance and were able to detect associated driving performance deficits including lateral deviation and accelerator control [71].

Akerstedt and coworkers have developed EEG measures for assessing sleepiness in transport operations with an early study comparing train drivers during day and night work, noting that EEG and EOG parameters (eye movements, eye closure) reflected severe subjective sleepiness at night. They noted EEG alpha bursts consistent with lapses when some drivers failed to act on signals, although later

research has shown that performance lapses may not coincide with microsleeps or other obvious EEG changes [72, 73].

EEG related techniques have included the use of event related potentials (ERPs) to assess sleepiness and decreased vigilance, with the P300 or late components being found sensitive to sleep loss, pathological sleepiness or assessment of "sleep inertia" after forced awakening [74, 75]. Other EEG components may be of use for future measures of sleepiness, particularly those linked to cognitive processing including error related positivity [76].

The development of neural nets or related advanced signal processing techniques with greater computer speed and power are enabling the development of real time analysis procedures that may be suitable for driver monitoring systems. For example, a simple EEG neural net system using simplified recording from behind the ears was able to distinguish variations in arousal compatible with driver safety monitoring [77]. These approaches will hopefully see the production of practical safety monitoring systems within the next decade.

Examples of the effects of driving during extended waking and during the circadian low point are given in Figures 3–5. These graphs plot changes in arousal based on physiological measures of driver state (EEG, EOG & EMG) against time recorded over two hours of driving. Figure 3. demonstrates typical day driving in the morning and after normal sleep. For around 80 minutes the driver maintains a

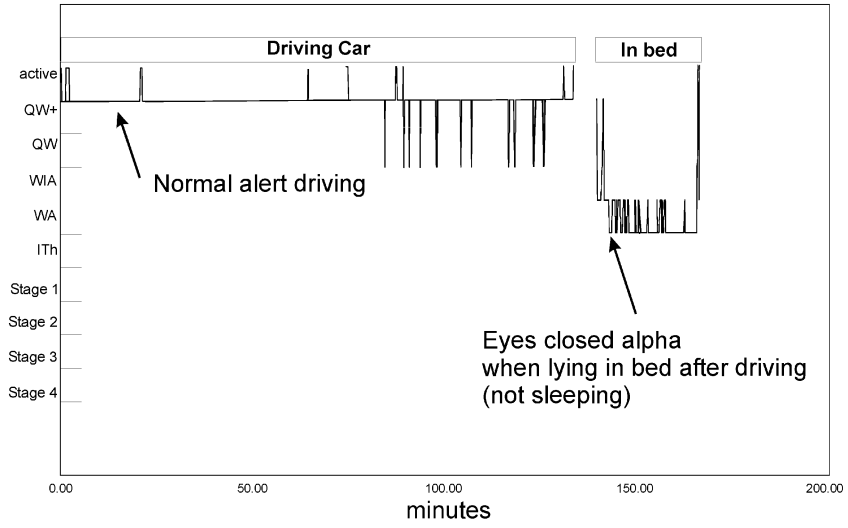

Figure 3 Morning day drive after normal sleep and subsequent sleep opportunity period. Physiological level of alertness based on EEG, EOG, EMG recording. Highest arousal is "active" with sleep shown as stages 1–4. Alert driving is maintained for over an hour, then brief periods of EEG alpha are seen reflecting lowered arousal and possible inattention (adapted from the author's data).

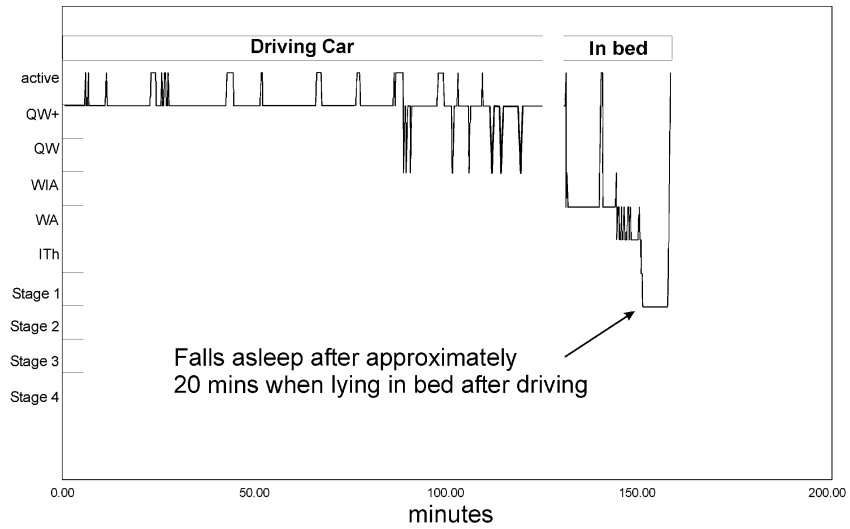

Figure 4 Evening drive after normal sleep and subsequent sleep opportunity period. Physiological level of alertness based on EEG, EOG, EMG recording. Highest arousal is "active" with sleep shown as stages 1–4. Alert driving is maintained for over an hour, then brief periods of EEG alpha are seen reflecting lowered arousal and possible inattention. After the drive the participant falls asleep when lying in bed reflecting circadian sleep tendency (adapted from the author's data).

good alertness level of "quiet waking plus" (QW+) with occasional brief bursts of "active" reflecting increased muscle activity and movement. The later part of the drive shows decreased arousal with brief dips of "waking with intermittent alpha" (WIA) reflecting bursts of alpha brainwave activity and lowered cortical arousal. Background sleep tendency or the homeostatic pressure to sleep was then assessed, with the driver attempting to sleep whilst lying in bed in the sleep opportunity period that followed. Although showing EEG drowsiness, the driver failed to fall asleep, showing that objectively they were not sleepy.

Figure 4 demonstrates a night drive ending before midnight, and whilst this is generally similar to the day drive, there is increased movement producing more "active" waking, which may represent a strategy for trying to maintain alertness. Increased sleep pressure or sleepiness is seen in the sleep opportunity period that follows, as the driver does fall asleep when in bed.

A typical early morning drive, when drivers are at their circadian low point, is plotted in Figure 5. Although a good arousal level is seen during the first hour, a significant deterioration then occurs with a marked loss of arousal and regular bursts of "intermittent theta" (Ith) or "microsleeps". The strong pressure for sleep

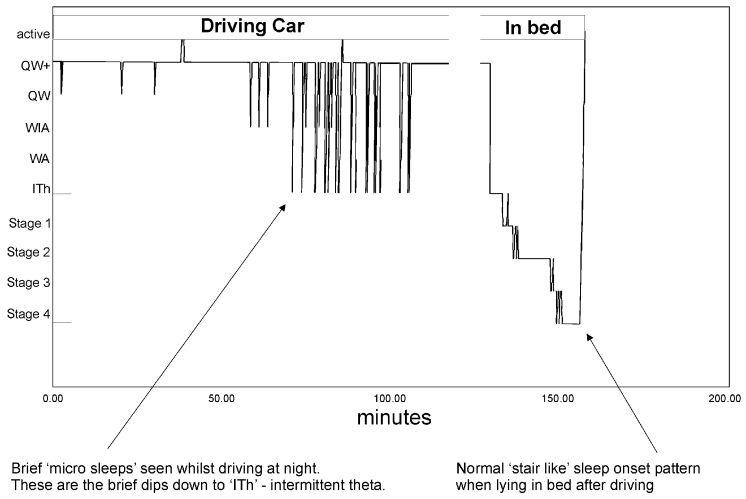

Figure 5 Night drive during early morning hours and subsequent sleep opportunity period. Physiological level of alertness based on EEG, EOG, EMG recording. Highest arousal is "active" with sleep shown as stages 1–4. Alert driving is maintained for an hour, but then the rapid onset of sleepiness is seen with the intrusion of EEG intermittent theta or "microsleeps". After the drive the participant falls rapidly and deeply asleep when lying in bed, reflecting the effects of extended waking and the circadian low point (adapted from the author's data).

reflecting marked sleepiness is then seen in the sleep opportunity period where slow wave sleep is seen.

Eye measures

A variety of eye measurements have been studied over the years including tracking eye direction, slow eye movements, blink rates and slow blinks including eye closure. Blinking was investigated over 50 years ago as a measure of attention, originally because of safety concerns, and blink rate was found to slow as attentional effort or cognitive demand increased [78]. This potential confound may explain why a recent review concluded that there were contrasting findings for the use of blink rate as a measure of sleepiness, although blink duration may be a useful measure of drowsiness [79]. Similarly, 20 years ago slow eye movements (SEMs) were considered to be inferior to EEG or behavioural measures in detecting sleep onset, although a recent study has shown them to be indicative of higher levels of sleepiness, but only when eyes are closed, limiting practical use [80, 81]. Again, blink

duration was proposed as a suitable candidate for detecting driver sleepiness by Hakkanen and colleagues, although a recent study has indicated general increases in both subjective sleepiness and lateral deviation with increased blink duration but pointed out that individual differences make this measure of questionable utility for driver warning systems [82, 83].

Eye tracking technology has now advanced to a stage where it can provide an unobtrusive measure of eye gaze direction and other parameters, including eye closure or blink duration. Companies such as "Smart Eye"® in Sweden are currently developing vehicle compatible systems that may be ready for production within a few years [84].

Performance measures

An argument against EEG and related physiological techniques is that they assess performance indirectly, through physiological assessment of the driver, and therefore rely on being accurate predictors of driver performance. Actual driving performance measures are potentially more useful, as they can detect a range of performance failures, not just sleepiness, including driver distraction or drug induced impairments. Lateral position (e.g. lane drifting) and accelerator control have already been mentioned in this overview. Variation in lateral position has been used successfully in the Netherlands for assessing drug induced impairments for over 20 years, and is described elsewhere in this volume.

Simpler performance measures have been used in the laboratory and in field testing, including the assessment of reaction time (RT) in Swedish drivers mentioned earlier. This study showed increases of around a tenth of a second in response times for young drivers who had driven eight or more hours; such increases may be critical in accident avoidance situations [53]. Simple RT may be used as a secondary task to driving in order to provide an indirect performance monitor, although performance tests may increase arousal or fail to accurately reflect driving performance [4, 46, 85]. Reaction time based tasks have also had mixed success, for example the psychomotor vigilance task (PVT) was considered amongst the most sensitive and reliable sleep related performance measures by Balkin and colleagues, although a recent study has found that PVT did not parallel sleepiness [73, 86]. Unfortunately, no single performance measure has emerged either as a "gold standard" for assessing sleepiness in the lab, or as a secondary task that is compatible with driver monitoring.

Subjective awareness and relationship with other measures

A number of studies have examined the relationship between subjective sleepiness, performance and physiological measures such as EEG. This has been particularly relevant when trying to examine whether one type of measure could predict another, and therefore of relevance for driver monitoring systems.

Some authors claim a good correlation between measures. In a 1998 editorial Akerstedt stated that he believed there was a correlation between subjective sleepiness, EEG changes and driver performance decrements, at least under certain conditions, and Baulk and Horne have claimed a high correlation between subjective sleepiness and EEG and that both these changed concomitantly with lane drifting [87, 88].

However, other authors have pointed out the large individual differences seen when comparing subjective sleepiness with performance [89]. Ingre and colleagues have written about the "ecological fallacy" that simple averages could not accurately predict absolute risk for individual subjects, when comparing simulated driving performance after night work with subjective sleepiness. They also found large individual differences for blink duration, subjective sleepiness and driving duration, whilst others have advocated the use of within subjects designs to assess sleepiness due to large individual differences [51, 79, 90]. The French study comparing reaction time performance of "vulnerable" and "resistant" participants after sleep deprivation has been mentioned earlier. The "resistant" participants maintained their performance across the night "independently of homeostatic pressure" reflected in increases in subjective and EEG sleepiness [52]. Another recent study found that subjective and objective measures factored out separately concluding that these different measures represented "distinct entities that should not be assumed to be equivalent" [86].

The most recent studies have therefore either suggested that individual differences are so large that comparisons of subjective sleepiness should not be compared with other measures using averages, or that there is no correlation between subjective sleepiness and driving performance or related measures. Murray Johns has also emphasised the situation specific nature of falling asleep and that "one situational sleep propensity is not always an accurate predictor of another, even in the same subject" [91].

These disparities may help to explain why people find it hard to predict when they will fall asleep as evidenced by the traffic accident figures. MacLean and colleagues point out the discrepancy in the literature regarding whether or not participants were aware of their levels of sleepiness and hence risk of accidents, supporting the previously mentioned study showing only 55% accuracy for predicting first sleep onset [4, 63]. Taken together, these findings indicate a clear need for functional warning systems and countermeasures.

Vehicle countermeasures – driver monitoring systems

The aim of researching different measures of driver sleepiness has been to assist the development of driver monitoring systems. A useful review is given by Williamson and Chamberlain, who include systems based on fatigue detection (e.g. EEG, eye gaze and closure), and driver performance measures which are based mostly on lane tracking (lateral position) and headway (distance to vehicle in front) [92]. Driver performance measures assess changes that are directly significant for road safety, and the Citroen C4 is given as an example. An option on this production car is to

have a seat that vibrates on the left or right depending on the side that the car crosses lane markings and therefore arouses the driver as well as giving error information.

Williamson and Chamberlain most favour multiple monitoring systems that can include both driver state and performance monitoring devices and cite the European Union "AWAKE" project that has produced a useful set of design guidelines for driver sleepiness warning systems. Generic driver assistance and warning devices that provide information to both facilitate driving and give safety warnings are also covered. They cite research that has looked at the acceptability of systems by users and note these include suggestions from drivers that safety warnings should be able to be turned off or volume attenuated, which would then reduce their effectiveness. However, drivers do favour the potential use of safety monitoring systems [4]. Clearly, driver education is a large part of acceptance of warning systems, including the need to be familiarised with the sound of infrequent but potentially startling alarms.

A key point is that driver warning systems should inform the driver when they are below safe operating levels. This is particularly important as they may not realise their current level of impairment, as reflected in the large number of sleep related vehicle accidents. Fatigue detection should be early enough to enable the driver to take suitable countermeasures such as stopping to drink coffee or take a nap. Problems cited for systems currently being developed include the late stage of drowsiness detected, focusing on measures of driver state rather than performance output, the effects of the system on driver performance and the timing and type of warnings used. They conclude by indicating more research and development is needed before effective devices are standard features in production vehicles. A recent review suggests that fatigue detection technologies may be able to reduce accident risk in the near future but echoes the need for further research to develop reliable indicators that can then contribute to unobtrusive fatigue detection devices [89].

Driver countermeasures

The key problems outlined include extended waking or driving, reduced sleep and working during the circadian low period. Clearly, education is of primary importance so that drivers are aware and can take appropriate steps to reduce their impact, including avoiding driving at vulnerable times if at all possible [4, 89]. Strategies for reducing the impact of driver sleepiness or fatigue have been included in a recent review. These include proper work and rest scheduling combined with good sleep hygiene. The use of appropriate pro-hypnotic medication and behavioural circadian rhythm adjustment strategies, such as controlling exposure to light where sleep time is available but sleep is then difficult to obtain, is also included. When inadequate sleep opportunities are available then limiting driving time, strategic napping and the possible use of alertness enhancing compounds can be considered [89].

Surveys of countermeasures employed by drivers have indicated a number of techniques. A German study from 50 years ago listed breaking the journey, caffeine consumption, sleeping longer and taking a short nap as the four most com-

monly used. Less effective and less frequently used methods included stopping and walking around the vehicle, smoking, talking, taking refreshments, radio, eating, conversation, opening the window, singing and taking a cold wash. Recent studies in Finland and Sweden of both lorry and general drivers have identified consuming coffee or other stimulant drinks, stopping and taking a short walk, napping, communicating with other drivers or passengers, smoking cigarettes, opening the window and listening to the radio as current practice. The Swedish study identified four groups of behaviours including stopping, coffee/caffeine, energy drinks and napping with the latter particularly used by drivers who had experienced sleep related accidents or severe sleepiness [4, 64, 93].

There seem to be relatively few scientific evaluations for most of these techniques, although cold air and radio have been studied by Reyner and Horne, who found that neither were as effective as caffeine or napping based on their earlier work, although radio provided some improvement for up to half an hour and sound has been reported as an effective countermeasure for truck drivers [94, 95]. Secondary tasks have also been considered as a method of increasing driver arousal but their acceptability has been questioned and a driving simulator study has shown that cortical arousal reflected in subjective and EEG changes was not associated with improved driving performance [4, 96].

Napping

Reviews suggest that napping can enhance waking performance and alertness after sleep loss or during circadian disruption, although the nap duration should not exceed half an hour to limit the effects of sleep inertia, which is worse after abrupt waking from slow wave sleep [97, 98]. The potential benefits of napping need to be weighted against the temporary decreases in alertness and performance that result from abrupt awakenings. The problem of sleep inertia was highlighted when aircraft were crashing into the sea after being launched from aircraft carriers in the Korean War and, though less critical, the impact of sleep inertia is of importance to driving. Whilst studies have shown deficits after waking from a normal eight hour sleep and that the duration of impairment may last up to four hours depending on task assessed, the effect does not generally extend beyond 30 minutes in the absence of sleep deprivation [99, 100, 101].

The potential benefit of relatively short naps is therefore worth considering as a countermeasure to driving sleepiness. Studies of shift work and driving have had mixed findings. For example, Gillberg and colleagues observed that neither a 30 minute nap nor rest pause improved simulated night truck driving, although Reyner and Horne did find that napping and caffeine improved driving performance in their simulator study [47, 102]. Napping taken during the night shift was found to improve response speed on a vigilance task at the end of the shift and a study of Italian police drivers found that those who did not take naps before night shifts had nearly a 40% increase in accident risk compared to those who did. The benefits of sleeping before night work have been endorsed in a recent review [89, 103].

Appropriate strategic napping can therefore be seen as a useful countermeasure to driver sleepiness and particularly for night driving, although nap duration should not exceed half an hour, and if driving under conditions of sleep restriction or extended waking, then a longer post waking period may be required to limit subsequent sleep inertia.

Bright light and melatonin

Given that driver sleepiness is worsened by shift work and night driving or other forms of circadian disruption it is logical to consider countermeasures that can help counteract phase shifts or improve sleep. Both bright light and melatonin synchronise the circadian clock by acting on the suprachiasmatic nucleus in the brain (SCN), and can be used separately or combined to induce phase shifting of human circadian rhythms [30, 104, 105]. The melatonin agonist Ramelteon has been shown to reduce sleep latency and a meta analysis found that melatonin also reduces sleep latency as well as increasing sleep efficiency and sleep duration. In comparison to conventional hypnotics, melatonin has also been shown to lack adverse withdrawal effects [30, 106, 107].

Melatonin was found to prevent day time reductions in sleep duration after simulated night shift work whilst bright light has facilitated adaptation to night shifts and re-adaptation to the daily schedule following night shifts [108, 109].

Appropriate use of hypnotics

The use of medication for insomnia and other medical conditions, as well as the use of stimulants are examined in other chapters, although brief coverage is included here in considering appropriate countermeasures and strategies for dealing with sleepiness and fatigue [89]. Where sleep is impaired due either to insomnia or sleep disturbance resulting from shift work and circadian disruption, then hypnotics can be beneficial in optimising available sleep time. The potential impairment due to residual hangover effects is a major concern for drivers, although newer hypnotics are much safer than the older benzodiazepines, with short acting compounds showing limited or no residual driving impairment next day, so that appropriate use of hypnotics can now be advocated and may be combined with waking caffeine during circadian sleep schedule reversal [89, 110, 111, 112, 113].

Caffeine and energy drinks

Caffeine has been shown to improve alertness, mood and performance after sleep loss, circadian desynchronisation or fatigue when performance is impaired [114, 115]. The use of coffee and other caffeinated beverages is popular amongst driv-

ers as a sleepiness countermeasure. Both laboratory and road driving studies have confirmed the benefits of caffeine after sleep deprivation or restricted sleep. These have included both 150 and 200 mg doses given as coffee, or 300 mg sustained release assessed during night road driving or with driving simulators in the daytime after sleep deprivation or restricted sleep. Combination with a brief nap of up to 15 minutes was found better than coffee alone [102, 116, 117].

Energy drinks, which often include caffeine amongst other constituents, have become increasingly popular over the last decade. From informal conversations we have noted that their use has become popular as a sleepiness countermeasure amongst drivers. Improvements in both mood and performance have been observed in laboratory studies during normal waking, and driving simulator performance has also been improved [118, 119].

The effects of caffeine in improving both mood and lateral position are shown in Figures 6 and 7. The study compared driving at midday and midnight in a simulator study comparing 200 mg caffeine given as coffee against placebo. Without coffee, subjective alertness was significantly reduced at midnight and lateral deviation was increased, whilst coffee reduced deviation to daytime levels [120].

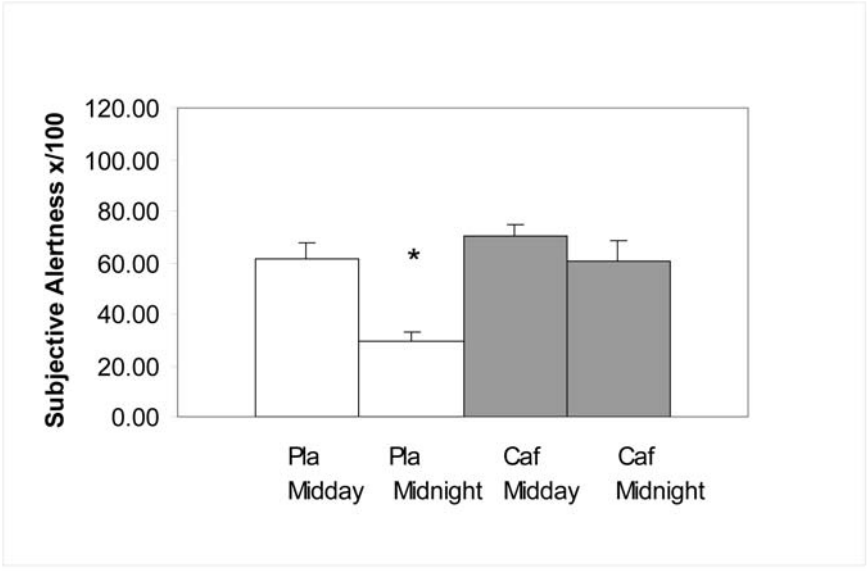

Figure 6 Subjective alertness comparing midday to midnight and the effects of 200 mg caffeine; (means, SEM, N = 12) higher scores represent being more alert. * $P < 0.05$ placebo *vs*. other treatments.

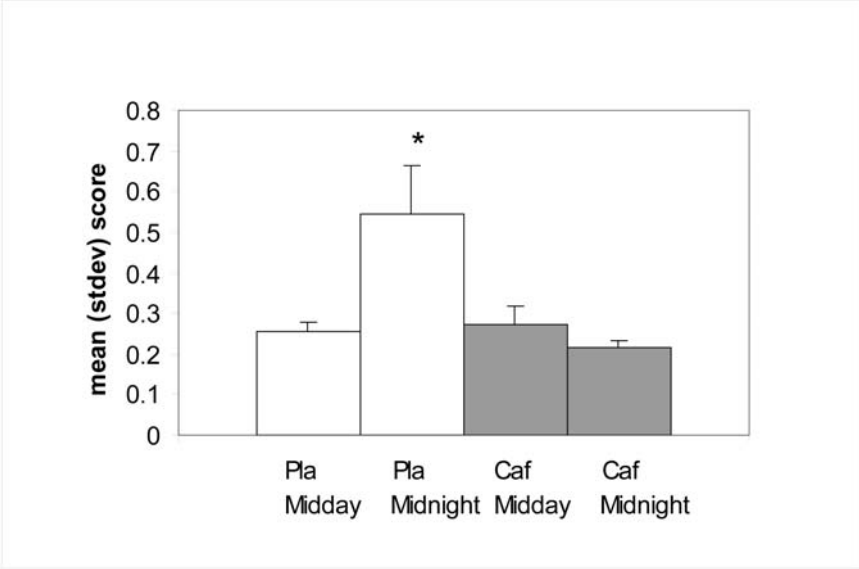

Figure 7 Lateral deviation on driving simulator comparing midday to midnight and the effects of 200 mg caffeine; (means, SEM, N = 12) higher scores represent poorer driving. P < 0.05 placebo *vs*. other treatments.

Conclusion

This brief review of countermeasures has highlighted the discrepancies found between subjective sleepiness and physiological measures including EEG, eye blinks or eye closure and other eye measures. There are changes in risk related to age and sex as well as marked individual differences which limit the use of specific measures as predictors of impending driver sleepiness and increased accident risk. Driver education and strategies to avoid or limit the impact of extended waking, sleep loss and driving during the circadian low are important. Direct performance measures of driver impairment are to be welcomed, although reliable commercially available warning systems are still some years away. Optimising sleep, the use of brief naps and caffeine are all useful in optimising driver arousal levels.

Future driving warning systems might usefully include both driver arousal state and direct performance assessment. Perhaps a driver "smart card" or similar system may be used to profile drivers storing their individual driver "signatures" and thus provide effective and reliable early warnings before driver accident risk due to sleepiness reaches a critical level.

Although the problem of sleep related accidents remains, valuable knowledge has been gained in the 20 years since Lauber's address calling for more research

and a better understanding of the role of driver sleepiness in vehicle accidents [1]. Whilst shift work and associated night driving has increased, we are now in a position to provide some practical countermeasures. Education is the most important step for both employers and employees so that the work environment and work schedules can be made to optimise functional waking levels and reduce or avoid working during critically low levels of arousal. This is particularly important for vulnerable groups including young drivers. Sleep can be maximised through pharmacological or other methods and similarly waking arousal levels can be enhanced. Taken together, these practical steps can have a significant impact on the numbers of vehicle accidents that are a result of driver sleepiness.

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Drugs, Driving and Traffic Safety
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Insomnia, hypnotic drugs and traffic safety

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Abstract

Sleep medication helps patients who suffer from insomnia to fall asleep and maintain asleep, but unfortunately hypnotic drugs often have residual effects that may affect daily activities such as driving a car. Epidemiological studies show that patients who use sleep medication are at increased risk of becoming involved in traffic accidents. These studies show an increased traffic accident risk for patients using benzodiazepine hypnotics or zopiclone.

This chapter reviews the experimental studies assessing the effects of various hypnotic drugs on driving ability. On-the-road studies confirm that benzodiazepine hypnotics and zopiclone significantly impair driving ability the morning following bedtime administration, whereas the Z-drugs zolpidem and zaleplon do not affect driving performance when taken as recommended. Impairment was dose dependent and most prominent in benzodiazepines with a relative long half-life.

Epidemiological studies show that tolerance to the impairing effects on driving ability of hypnotic drugs develops slowly. However, experimental evidence from on-the-road driving studies on the effects of chronic use of hypnotics is currently lacking. Also, the impact of untreated insomnia on driving should be examined in future studies.

Current hypnotics all act at the GABA receptor which may explain their residual effects on driving performance. Various newly developed hypnotic drugs have a different mechanism of action and may therefore be devoid of residual effects on driving performance.

Introduction

Insomnia is the inability to fall asleep or to maintain sleep during the night. People who suffer from insomnia may, therefore, have fewer hours of sleep during the night and often fragmented sleep, characterized by several awakenings during the night. As a result, people with insomnia often are sleepy during the day. Sleepiness may result in reduced attention and affect daily activities such as driving a car.

Surveys show that insomnia is a common disease affecting approximately one-third of the general population [1]. Insomnia is often a co-morbid disorder accompanying other diseases such as depression or anxiety [2].

Although non-pharmacological strategies, such as cognitive behavioral therapy, are increasingly being implemented in the treatment of insomnia, pharmacotherapy is still the most frequently used treatment for insomnia [3]. The primary choice of sleep-enhancing medication is sedative hypnotics, such as benzodiazepines and the newer benzodiazepine receptor agonists zopiclone, zolpidem and zaleplon [4]. However, prescription of antidepressants for the treatment of insomnia has increased over the last decade, which may be the result of frequent reports of adverse effects and drug dependence due to benzodiazepines [5].

Benzodiazepines

On-the-road studies have been performed to examine the residual effects of hypnotics on driving ability. Subjects drove 100 km on a public highway in normal traffic while maintaining a constant speed and lateral position within the right traffic lane. The primary parameter in driving is the Standard Deviation of Lateral Position (SDLP). The weaving index SDLP is a measure of vehicle control: with less control, SDLP increases. Figure 1 summarizes the results of six studies [6–10] that examined the effects of benzodiazepine hypnotics on driving ability. SDLP increments relative to placebo are shown.

Most studies were performed in healthy female subjects with a history of insomnia and benzodiazepine use. Tests were performed after one or two nights of treatment administration, in the morning (10–11 hours after bedtime intake) or in the afternoon (16–17 hours after intake). These times were chosen because they compare to the times that people drive to work in the morning and back home in the afternoon. Figure 1 also shows levels of impairment that were observed with three blood alcohol concentrations (BAC), corresponding to the most common legal limits for driving a car [11].

Flurazepam

Three studies were performed to examine the residual effects of flurazepam on driving ability [6, 9, 12]. In 24 female subjects, both 15 mg and 30 mg flurazepam

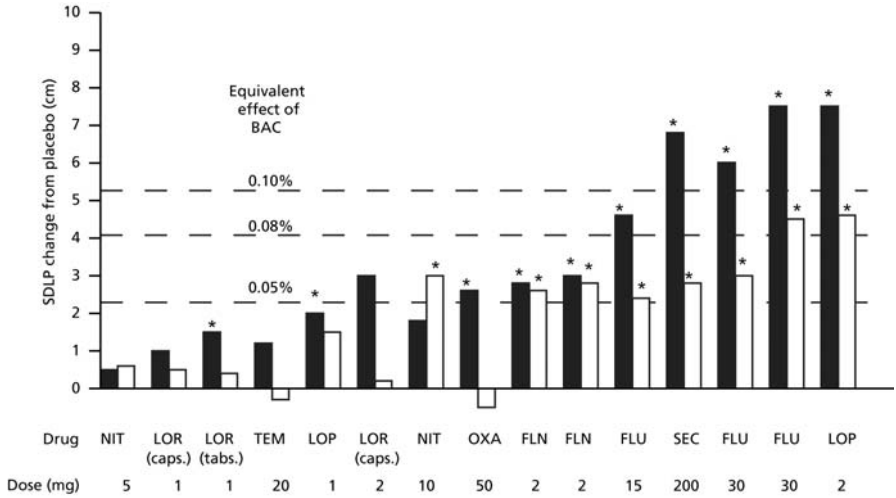

Figure 1 Benzodiazepine hypnotics and driving performance. Standard Deviation of Lateral Position (SDLP) increments relative to placebo are shown. Driving tests were performed in the morning (white bars) and afternoon (black bars) (10–11 and 16–17 h after bedtime administration, respectively). Significant differences from placebo are indicated by an asterisk, dotted lines indicate levels of SDLP increment observed with most common legal blood alcohol limits for driving a car. NIT, Nitrazepam; LOR, lormetazepam; TEM, temazepam; LOP, loprazolam; FLN, flunitrazepam; FLU, flurazepam.

severely impaired driving performance the morning following bedtime administration [6, 12]. In the afternoon, 16–17 hours after intake, driving performance was also significantly impaired [6]. Four subjects used the 30 mg treatment for one week. After eight nights, driving was still impaired in the morning session. The latter finding was confirmed in a larger sample (16 females): driving was impaired the morning following two, four and seven nights of treatment with flurazepam 30 mg [9]. Impairment, relative to placebo, with flurazepam 15 mg equaled that observed with blood alcohol concentration above 0.08 %.

Flunitrazepam

Two studies showed that flunitrazepam (2 mg) significantly impaired driving performance in the morning and afternoon after two treatment nights [6–7]. In both sessions, driving impairment was comparable to that observed with a BAC of 0.05 %. Surprisingly, another study failed to find significant effects of flunitrazepam 2 mg after a single night of treatment [13]. Nevertheless, results of the driving simulator and closed road studies support the fact that performance is impaired the morning following intake of 1 or 2 mg flunitrazepam [14–15].

Nitrazepam

Two studies examined the effects of nitrazepam on driving ability. The 5 mg dose did not affect driving performance in 16 female subjects [7]. The second study showed that the 10 mg dose of nitrazepam significantly impaired driving after two nights of treatment [8]. Interestingly, impairment in the afternoon was more pronounced than in the morning session. This illustrated the impact of active metabolites; in hypnotics without active metabolites impairment is more pronounced in the morning session. After four and seven nights of treatment, 10 mg nitrazepam did not significantly impair driving, suggesting that tolerance develops after repeated treatment.

Lormetazepam

Lormetazepam is available as a tablet and soft gelatine capsule. Both formulations have been tested on the road. In 16 females, 1 mg lormetazepam (soft gelatine capsule) did not significantly impair driving performance the morning following two, four and seven treatment nights [9]. The 2 mg dose did cause significant impairment. A study in 18 healthy men showed significant impairment after treatment with a 1 mg lormetazepam tablet after one or two treatment nights [10]. Impairment was relatively slight (comparable to that observed with a BAC less than 0.05%) and not found in a driving simulator. A more recent driving simulator study in 12 healthy volunteers also found no significant effects the morning following bedtime administration of 1 mg lormetazepam [16].

Oxazepam

Oxazepam (50 mg) significantly impaired driving performance in 18 healthy men after one and two treatment nights [10]. Impairment was comparable to that observed with a blood alcohol concentration of 0.05%. In the afternoon, driving was not affected. Subjects also performed a driving simulator test, but no significant effects were found.

Loprazolam

Loprazolam (1 mg) significantly impaired driving performance in the morning, but not in the afternoon [6]. Twice the recommended dose (2 mg) also showed significant impairment in the afternoon driving session. Impairment in the afternoon session was comparable to that observed with a BAC greater than 0.10%.

Temazepam

Temazepam (20 mg) did not affect driving performance after two, four and seven nights of treatment [8]. Another on-the-road study [15] reported that driving performance after one and seven nights of treatment improved in patients with insomnia. A closed road study did show impairment 12 hours after intake of temazepam (20 mg): healthy female subjects had more collisions when maneuvering passable and non-passable gaps on the circuit. No effects were reported on a weaving test between bollards [17].

Other benzodiazepine hypnotics

Triazolam and brotizolam are relatively short acting benzodiazepines. Up to now, they have not been examined using the on-the-road driving test. In a driving simulator and a closed road circuit, triazolam (0.25 mg) did not significantly impair performance [18]. Also, on a monotonous driving simulator test, brotizolam (0.25 mg) did not impair performance [19].

Summarizing the data: results of a meta-analysis

Results from a recent meta-analysis [4] confirm that benzodiazepine hypnotics and zopiclone significantly impair driving performance the day following bedtime administration, whereas zolpidem and zaleplon do not (see Fig. 2).

Six studies, published from 1984 to 2002, were included in the meta-analyses [6–10]. The morning following bedtime administration, i.e. 10–11 hours after dosing, significant driving impairment was found for the recommended dose of various benzodiazepine hypnotics (ES = 0.42; 95 % Confidence Interval (CI) = 0.14 to 0.71). Twice the recommended dose of benzodiazepine hypnotics impaired driving both in the morning (ES = 0.68; CI = 0.39 to 0.97) and afternoon, i.e. 16–17 hours after dosing (ES = 0.57; CI = 0.26 to 0.88).

Non-benzodiazepine hypnotics: the z-drugs

Given the adverse effects of benzodiazepine hypnotics, the search for new hypnotics continued and resulted in the development of the so-called z-drugs: zopiclone, zolpidem and zaleplon. Although these drugs also act at the GABA receptor, they do so in a much more specific way than the benzodiazepines. In addition, they have a relatively short half-life.

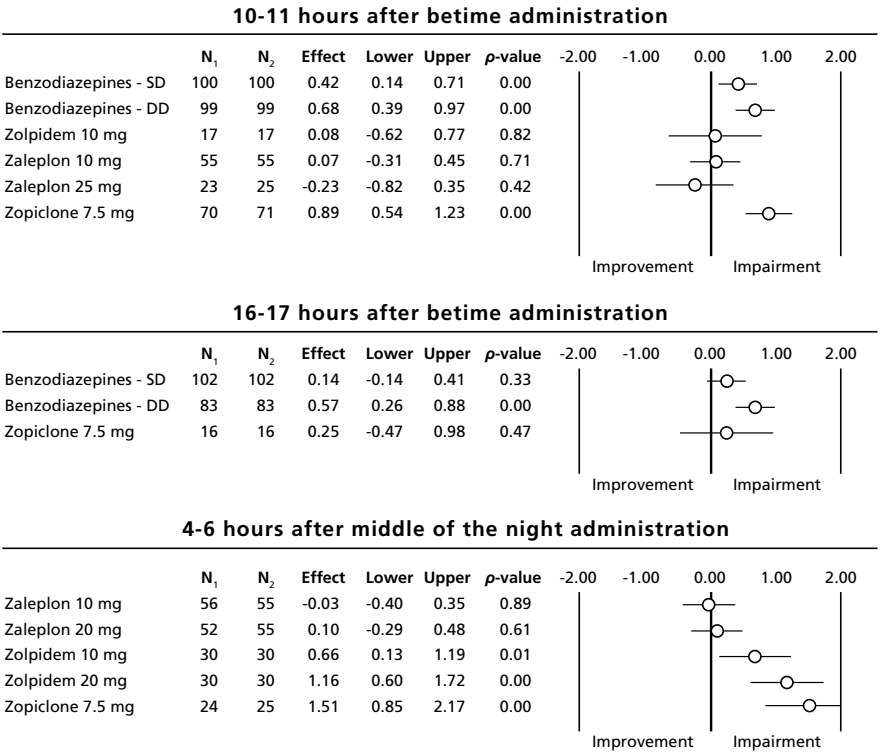

Figure 2 Results from the meta-analysis.The effects are significant ($p < 0.05$) if the 95 % Confidence Interval (CI) is greater or smaller than 0. Abbreviations: SD = single dose, DD = double dose, N1 = treatment, N2 = placebo, Lower = lower limit of the 95 % CI, Upper = upper limit of the 95 % CI. Adapted with permission from reference [4].

Zopiclone

Three studies have been performed to examine the effects of zopiclone 7.5 mg on driving performance. Significant driving impairment was reported by all studies [7, 12, 20]. The magnitude of impairment (3 to 8 cm increment of SDLP relative to placebo) was comparable to that observed after intake of benzodiazepines and higher than what is regarded as acceptable after intake of alcohol (2.4 cm with a BAC of 0.05 %). Epidemiological research reported a four-fold increase in traffic accident risk for those using zopiclone [21]. In terms of traffic safety, zopiclone is no improvement.

Zolpidem

Research showed that zolpidem (10 mg) when taken as recommended did not affect driving performance [13]. However, when taken in the middle of the night, or at a

higher dosage than recommended (i.e. 10 or 20 mg, 4 hours before driving), performance on the driving test was significantly impaired [22]. Recent reports on misuse of zolpidem are also a reason for concern: an increasing number of traffic accidents have been related to the misuse of zolpidem [23].

Zaleplon

Zaleplon (10 and 20 mg) does not significantly impair driving performance 10–11 hours after intake [12, 20]. Even when administered during the night and at higher dosages than recommended (i.e. 20 mg, 4 hours before driving) no significant impairment was found [22].

Factors affecting driving ability

Half-life

Benzodiazepines vary greatly in half-life. Benzodiazepines with a long half-life are present in the blood for a longer time and thus may have an extended negative effect on driving performance. Table 1 gives an overview of the half-life of different benzodiazepine hypnotics. Benzodiazepines with the longest half life have the greatest negative effect on driving [24]. When time after administration increases, the effect on driving performance decreases. This is also evident in Figure 1: in the afternoon SDLP increments are less pronounced when compared to the morning driving tests (except for nitrazepam in which its metabolites have a much more pronounced effect on driving than the drug itself).

Also, several drugs have active metabolites. For example, flurazepam and its metabolites have a half-life up to 100 hours. These active metabolites may also have a negative effect on driving. Epidemiological evidence [25] confirms that traffic accident risk is significantly higher for users of benzodiazepines with a long half-life.

Dose

With increasing dosages, the effect on driving ability is more pronounced. This is evident from Figure 1.

Epidemiological evidence confirms that dosage is important in determining the magnitude of accident risk. For example, Ray et al. [26] reported significantly increased traffic accident risk for users of benzodiazepine hypnotics (OR = 1.5, 95% CI 1.1–2.0). This effect was most profound for high dosages (comparable to more than 20 mg diazepam daily) and significant (OR 2.4, 95% CI 1.3–4.4). Low dosages (comparable to less than 4 mg diazepam daily) showed no significant effect (OR = 1.1, 95% CI 0.5–2.2).

Table 1 Drugs used in the treatment of insomnia (reproduced with permission from reference [24]).

	Dose (mg)	T1/2 (h)	Tmax (h)	Active metabolite(s)
Benzodiazepine hypnotics				
Triazolam	0.25	1.5-5.5	1	+
Temazepam	20	7-11	0.8	–
Loprazolam	1	8	2-5	–
Lormetazepam	1	10	1-2.5	–
Flunitrazepam	2	16-35	1.2	+
Nitrazepam	5	18-34	2	+
Flurazepam	30	47-100	0.5-2	+
Non-benzodiazepine hypnotics				
Zopiclone	7.5	3.5-6.5	1-2	–
Zolpidem	10	1-2	0.5-1	–
Zaleplon	10	2-4	0.5-1	–
Benzodiazepine anxiolytics				
Oxazepam	50	4-15	2-3	–
Alprazolam	1	12-15	1-2	–
Diazepam	10	20-100	1-2	+
Lorazepam	2.5	12-16	2	–
Clonazepam	0.5-2	30-40	0.5-1	–
Antidepressants				
Amitriptyline	50-100	12-36	1.5	+
Doxepine	150	33-80	2	+
Trazodone	25-150	8	1-2	+

+ = active metabolites; - = no active metabolites

Individual differences

Figure 3 shows SDLP increments relative to placebo 4 hours after administration of zaleplon and zolpidem [24]. Both hypnotics were administrated in the recommended dose (10 mg) and twice the recommended dose (20 mg). Individual subjects can be identified by numbers in Figure 3. Note that not all individuals are equally sensitive to the effects of zolpidem or to administering twice the recommended dose.

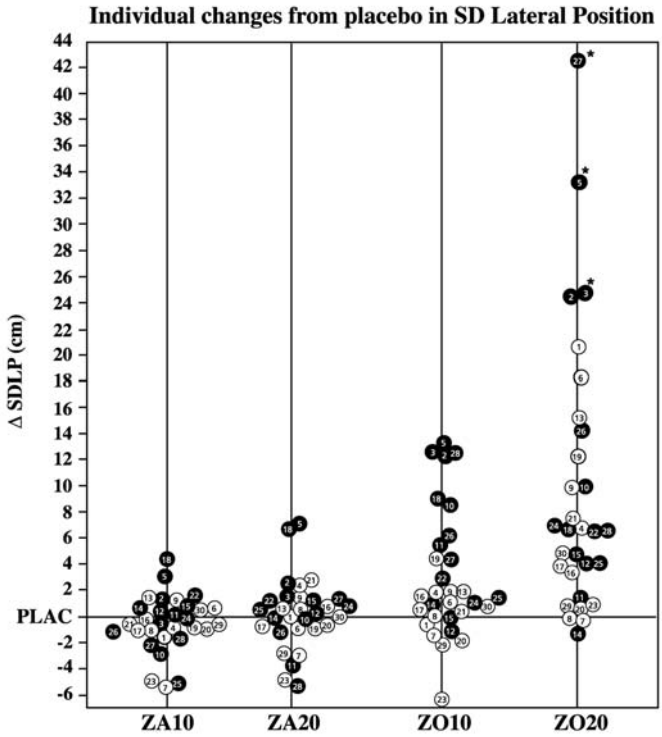

Figure 3 Individual SDLP differences relative to placebo 4 hours after intake of zaleplon 10 mg (ZA10), zaleplon 20 mg (ZA20), zolpidem 10 mg (ZO10), and zolpidem 20 mg (ZO20). Black circles are women, white circles are men. Numbers indicate the subjects. (reproduced with permission from reference [24]).

Most subjects show a modest performance decrement when increasing the dosage; whereas some show no further aggravation of performance and others show a great decrease in driving performance.

Gender and age

Figure 3 also illustrates differences in women (black circles) and men (white circles). In the zolpidem 20 mg condition women drove significantly worse then men. Also, subjects that had to stop their driving test due to unsafe driving (indicated by an asterisk) were all female. This finding is typical for many driving studies [5, 24]. Sleep pills come in standardized dosages that do not take into account biological differences in men and women (e.g. weight and differences in water/fat distribution). Hence, women are often more sensitive to standardized dosages when compared to men.

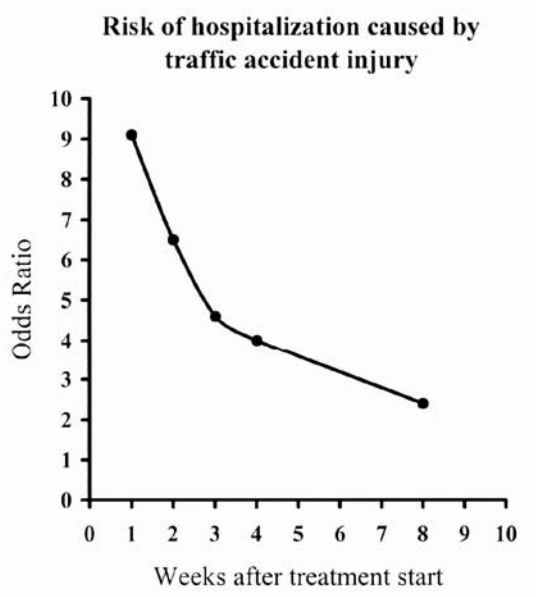

Figure 4 Traffic accident risk after treatment with flurazepam and triazolam (reproduced with permission from reference [24]).

Standardized dosages also may be problematic in the elderly. As a solution, the elderly are often prescribed half the recommended dose of younger adults. On the road studies have not yet been performed in elderly subjects, which should be an important aim of future driving studies.

Tolerance

After repeated daily use, the residual effects of hypnotic drugs may become less pronounced. This tolerance, however, develops slowly and is often not seen with intermittent (as needed) use. An example where tolerance gradually reduced traffic accident risk was reported by Neutel [27]. Neutel followed about 80,000 patients using triazolam or flurazepam. The data were compared to approximately 100,000 healthy control subjects. Traffic accident risks were high after treatment initiation, but became gradually less after some weeks. This is illustrated in Figure 4. After eight weeks of treatment, patients using benzodiazepines still had a traffic accident risk that was more than twice that of the healthy control subjects.

Epidemiological evidence [25] showed that, up to one year of treatment, the risk of having a traffic accident was still significant (OR 1.26, 95% CI 1.09–1.45) in elderly drivers using long half-life benzodiazepine hypnotics. For those taking benzodiazepines with a short half-life the likelihood of being involved in a crash was not significant.

Discussion

This chapter shows that most current hypnotic drugs have a negative impact on driving ability. The benzodiazepine hypnotics and zopiclone in particular have residual effects that may last during the next day. The magnitude of impairment depends on various factors including half life, dosage, gender, age and the development of tolerance. Zolpidem can be used safely if patients follow the instructions for usage. That is, take the recommended dosage (10 mg) immediately before bedtime and allowing 8 hours of sleep. Studies with zaleplon did not report negative effects on driving performance.

Unfortunately, effects of insomnia itself have not been investigated using the on-the-road test. Another limitation is that the effects of long-term use of hypnotic drugs have not been investigated. Epidemiological evidence shows that tolerance develops after daily use, but also points at increased traffic accident risk that may persist for months after treatment initiation. Epidemiological data on zolpidem and zaleplon is currently lacking. Furthermore, driving studies have not yet been performed in the elderly. Given that this group is overrepresented in the patient population, future studies should be performed in the elderly as well. In addition, gender differences in sensitivity to the effects of hypnotics should be elucidated by future research. Most of the studies discussed in this chapter have a sample size that does not allow comparisons between men and women. Future driving studies with larger sample sizes should be conducted to enable this comparison.

New sleep medication is currently in development or has recently been marketed. Examples are indiplon, a new sleep drug that also acts at the GABA receptor, or ramelteon and melatonin, that act at melatonin M_1 and M_2 receptors. Newly developed hypnotics with a mechanism of action that is not associated with the GABA receptor may be promising in that they may be devoid of residual effects on driving ability.

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Drugs, Driving and Traffic Safety
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Drugs, driving and traffic safety in sleep apnea

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Abstract

Sleep apnea affects 2–4% of the population. It is characterised by repetitive episodes of brief upper airway obstruction during sleep, with associated arousal from sleep. Consequences of untreated sleep apnea include excessive daytime sleepiness and impaired cognitive functioning and driving performance. Sleep apnea is also associated with a number of co-morbidities, including hypertension, insomnia and cardiovascular disease. As such, many sleep apnea patients are on medications that can potentially affect their sleep apnea severity and daytime functioning, including driving performance. Centrally-acting depressant drugs, including alcohol, antihypertensives, narcotics and sedatives, can cause respiratory depression and worsen sleep apnea. They may increase sleepiness and further impair driving performance either through direct actions on the central nervous system or through increasing sleep apnea severity. This chapter describes the effects of sleep apnea on daytime sleepiness, cognitive functioning and driving performance, as well as the drugs affecting waking and nocturnal respiration.

Introduction

Sleep apnea is a common condition, which affects between 2% and 4% of the population [1]. It is characterised by repetitive episodes of brief upper airway obstruction during sleep, with associated arousal from sleep. Consequences of untreated sleep apnea include excessive daytime sleepiness, impaired cognitive functioning and simulated driving performance. Additionally, sleep apnea patients have a higher road crash risk than the general population. Sleep apnea is also associated with a number

of co-morbidities, including hypertension, insomnia and cardiovascular disease. As such, many sleep apnea patients are on medications that can potentially affect their sleep apnea severity and daytime functioning, including driving performance. Centrally-acting depressant drugs, including alcohol, anti-hypertensives, narcotics and sedatives, can cause respiratory depression and worsen sleep apnea. They may increase sleepiness and further impair driving performance either through direct actions on the central nervous system or through increasing sleep apnea severity. Alcohol in combination with sleepiness results in severe driving performance impairment, even at low levels. Direct examination of the combined impact of these drugs on driving performance in sleep apnea patients is limited. However, there is evidence that sleepiness related to sleep apnea, alcohol and some psychoactive drugs have independent effects on crash risk. Further research is required to clearly define the risks associated with alcohol use and psychoactive drugs in sleep apnea. However, it would be prudent to avoid their use in untreated sleep apnea patients and use them cautiously in those on treatment.

Sleep apnea causes sleep disruption and reduces blood oxygen levels at night, which can cause sleepiness and impair daytime functioning and driving performance. Drugs may alter the severity of sleep apnea. Importantly, drug use may also exacerbate daytime impairment in sleep apnea, thus affecting driving and potentially increasing crash risk. The following chapter will describe the disorder sleep apnea and its' negative effects on daytime sleepiness, cognitive functioning and driving performance, including motor vehicle crash risk. It will then outline the different drug classes that may affect waking and nocturnal respiration. Finally, we will describe the effects of both sleep apnea and drugs on daytime sleepiness, cognition, and driving.

Sleep apnea physiology

Sleep apnea is a common condition that can result in excessive sleepiness, impaired neuropsychological function and increased risk of road crashes and industrial accidents. It affects between 2 % and 4 % of the adult population [1], although other studies suggest that up to 10 % of adults show some symptoms regularly [2]. Sleep apnea may occur as a result of obstruction in the upper airway or reduced drive to breath. These features may occur in isolation in individuals, but can be considered to represent a continuum of destabilized ventilatory control [3]. Obstructive sleep apnea (OSA) is characterized by obstruction of the upper airway and the presence of continued respiratory effort with normal central nervous system drive for respiration [4]. Repetitive brief upper airway obstruction occurs during sleep, resulting in apneas (complete cessation of breathing) or hypopneas (a reduction in breathing; Figure 1) [5]. This occurs as a result of anatomical narrowing in the pharynx and a reduction in tone in the upper airway muscles that normally help to keep the upper airway open during sleep. Anatomical narrowing of the pharynx may occur as a result of skeletal abnormalities, such as retrognathia (recessive jaw). Excessive

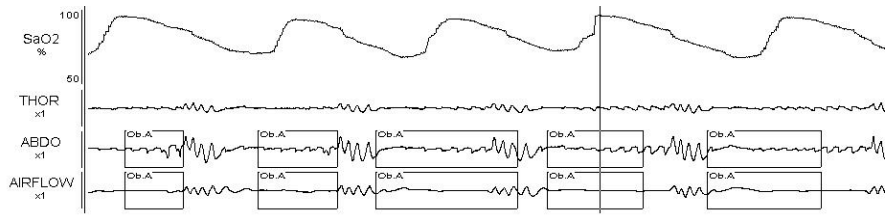

Figure 1 Polysomnography trace of an individual with OSA over a five-minute period. Blue squares indicate where an apnea has occurred. Apneic events are associated with a reduction or cessation of airflow from the nose, reduced abdominal and chest wall movement (ABDO and THOR traces) and a subsequent reduction in oxygen saturation (SaO_2).

Note: SaO_2 = oxygen saturations; THOR = thoracic band; ABDO = abdominal band

soft tissue may also result in anatomical narrowing, as occurs with obesity, tonsillar enlargement or upper airway tumours. Apneas and hyponeas often terminate with arousal from sleep, with resultant fragmentation of sleep and reduction in total sleep time [6]. They are also associated with a variable degree of hypoxaemia (reduced oxygen concentration in the blood). These features account somewhat for the daytime functional impairment that occurs in obstructive sleep apnoea.

Hypoxia as a result of OSA may cause cortical damage, as it creates a suboptimal environment for the restorative cellular processes that occur during sleep. Focal neuronal loss has been observed in OSA in areas associated with cognitive impairment. In an initial study OSA was associated with an 8 % loss of grey matter concentration within the left hippocampus in a small group of patients [7]. These early findings have recently been confirmed and extended, showing more extensive loss of grey matter bilaterally in the parahippocampus in a group of 22 OSA patients [8]. Two further studies have investigated brain structure in OSA using functional magnetic imaging [7, 9]. Whilst Macey et al. found diffuse structural abnormalities, O'Donoghue et al. found fewer abnormalities. The inconsistency between the studies may be due to the use of different analysis techniques and thresholds, plus inclusion of patients with co-morbidity. Cortical neuronal damage may account for some of the neurocognitive and driving performance deficits observed in OSA patients.

In contrast to OSA, central sleep apnea (CSA) is characterized by unstable ventilatory control with short periods of absent or reduced central nervous system drive to breath. This results in periods of reduced or absent respiratory muscle activity and hence reduced or absent respiration [10]. CSA occurs in healthy people at high altitudes. It also occurs in relation to severe obesity, some drugs (e.g. narcotics), cardiac failure and central nervous system damage (e.g. stroke, tumour and trauma). However, it makes up less than 10 % of people presenting with sleep apnea [10]. Obstructive and central sleep apnea may occur in the same individual (mixed apnea) and even during the same apneas or hypopneas. CSA and mixed apnea also cause arousals from sleep and hypoxaemia, resulting in impaired daytime function.

The rationale therefore for treating OSA stems from the increased risk of comorbidities, such as hypertension and cardiovascular disease, and the consequences of excessive daytime sleepiness, which can lead to road and workplace accidents. Treatments for OSA are predominantly aimed at reducing airway obstruction. They include; weight loss; nocturnal nasal continuous positive airway pressure (CPAP); pharyngeal surgery; oral devices to physically prevent airway collapse (such as mandibular splints); reducing alcohol intake; adjustment to sleeping position; and pharmacological treatment. Currently, the most widely utilized and most effective treatment is nasal CPAP. This treatment works by producing a positive airway pressure *via* a facemask to counteract the subatmospheric collapsing pharyngeal pressure produced during an obstructive apnea [11]. The main issue with this treatment is poor patient compliance, and therefore the success of this treatment relies on the willingness of patients to wear the mask each night. When used correctly, CPAP has been shown to reduce apneas and hypopneas, and eliminate oxygen desaturation [12]. Studies have also demonstrated improvements in daytime sleepiness following CPAP treatment, including self-reported [12] and objectively assessed [13, 14] daytime sleepiness. Treatment of OSA with CPAP has also been shown to improve driving performance and reduce crash risk [15, 16].

Consequences of sleep apnea

Sleepiness

OSA is associated with excessive sleepiness and deleterious effects on health, cognitive function, and quality of life. Stroke, hypertension, depression, and ischaemic heart disease are related to OSA [17–20]. Chronic excessive sleepiness occurs as a result of frequent arousal from sleep and reduced total sleep time, with an increased tendency to fall asleep during daily activities [21]. Moderate to severe sleepiness on the Epworth sleepiness Scale has been demonstrated in people with OSA in both clinical and general populations [22, 23]. OSA patients report frequent episodes of sleepiness whilst driving and often need to stop driving because of sleepiness [24].

In the laboratory, people with moderate to severe OSA fall asleep faster then people without OSA [25]. In a group of patients with predominantly severe OSA the average time to fall asleep was markedly reduced (2.6 minutes) compared to a matched control group (12.9 minutes) on the multiple sleep latency test [26]. This increased sleep tendency has been demonstrated in truck and bus drivers with OSA [27, 28]. The latter of these studies also demonstrated increased blink duration whilst driving in bus drivers with OSA [29]. Studies assessing the relationship between mild OSA and sleepiness in the laboratory, have found more variable results however [30, 31]. A reduction in sleepiness has been demonstrated in the laboratory following treatment of OSA with nasal CPAP in patients from general populations [32, 33] as well as professional drivers [29]. Improved subjective sleepiness has also been found in controlled treatment studies of OSA [34, 35].

Cognitive impairment

A variety of neuropsychological functions are impaired in sleep apnoea sufferers, including memory, learning and executive function [30, 36–38]. Moderate and severe sleep apnoea is clearly associated with impaired performance on vigilance tasks, with lapses in attention and slower reaction times [13]. Studies of mild disease have found more variable results [30]. Powell compared reaction times in subjects with mild to moderate OSA to those in normal subjects at different blood alcohol concentrations [39]. Reaction times for all OSA subjects were slower than those measured for control subjects at a mean blood alcohol concentration of 0.057 g/dl, suggesting that vigilance was worse in OSA subjects than that at a blood alcohol level that is known to increase accident risk. Lapses in attention during a vigilance task have also been demonstrated in commercial vehicle drivers with OSA [28]. The degree of hypoxaemia and sleep fragmentation at night and sleepiness during the day are all related to impaired vigilance in OSA subjects [38, 40, 41].

Simulated driving performance

Most studies evaluating driving skills have used laboratory measures, rather than on-road driving assessment. Virtually all have found that performance on simulated tracking and driving tasks is impaired in people with OSA. Findley compared performance on two driving tasks between a group of subjects with severe OSA and a control group [42]. On one task subjects had to avoid obstacles on a road by using computer keys to change lanes. Those with OSA hit an average of 44 objects in 30 minutes, compared to nine in the control group. In the second driving task they had more errors for signalling, braking, accelerating and steering. George found greater tracking error and slower reaction times in OSA subjects, with their performance worse than that of control subjects who had ingested alcohol (mean blood alcohol concentration 0.09 %) [43]. In a subsequent study, performance on the tracking task improved markedly in OSA subjects on nasal CPAP, with incomplete improvement on the vigilance task [44]. These and other studies of driving simulation [45–47] have involved patients with severe sleep disordered breathing compared to normal controls. One study has assessed the relationship between driving performance and OSA in professional drivers [28]. Driving performance was related to severity of OSA, but performance deterioration was only evident for subjects with moderate to severe disease.

Treatment of OSA improves impairment on vigilance and driving tasks, although most studies suggest that performance does not return to normal levels. In subjects with mild to severe OSA nasal CPAP improved performance on a vigilance task compared to a placebo condition [33]. Studies in patients with mild OSA have not shown significant benefit however [12, 36]. Nocturnal nasal CPAP therapy also reverses most, but not all, of the driving impairment evident in subjects with OSA [42, 44, 48–50]. These studies have shown marked improvement in tracking error, frequency of driving off the road and response times to target stimuli in divided

attention driving tasks, suggesting that OSA is a direct cause of impaired driving performance.

In summary, moderate to severe OSA is associated with impaired vigilance and driving performance. The degree of impairment is similar to that at high blood alcohol levels, which are associated with increased road accident risk. These changes are present both in clinic and general populations. There is relatively little evidence to suggest that vigilance is impaired in those with mild OSA, however. Only one study has assessed vigilance and driving performance in professional drivers with OSA, but results were similar to the general population studies. Treatment with nasal CPAP improves vigilance and driving performance, but does not return it to normal in all subjects.

Sleep apnea and road crashes

Untreated OSA is associated with a two to eight-fold increased risk of road crashes, as well as impaired driving performance [51–53]. A recent study [54] estimated that 800 000 OSA-related motor vehicle accidents (MVAs) occur annually in the US at a cost of US$15.9 billion and 1,400 lives lost. Sleepiness from all causes is estimated to be responsible for approximately 20% of MVAs. In middle age (30–60 yrs) drivers, OSA is likely to be a prominent cause of sleepiness-related crashes.

Findley compared road crash records from 29 patients with OSA to those of matched control subjects and statistics for the state of Virginia, USA [55]. Of the patient group, 31% had had an accident in the previous five years, compared to 6% of control subjects. There was a sevenfold increased crash rate in patients compared to controls and two and a half times increase in the rate compared to the state average. Three subsequent case-control studies found similar associations between OSA and road crashes [56–58] (Table 1). Professional drivers have been found to have a high prevalence of OSA [59–61]. In a large cohort of professional drivers, those with symptoms of obstructive sleep apnea syndrome had a higher risk of any crashes, and of a single vehicle crashes (OR 1.63, 95% CI 1.08–2.48) [60].

Increased crash risk does not appear to be closely related to the severity of OSA, although some studies have suggested that it is predominantly patients with severe OSA who have an increased crash risk. George (1999) found that the average crash rate was 0.12 per year in those with severe disease (RDI > 40) compared to 0.07 per year in control subjects. There was only a minor increase in crash rate in patients with lesser degrees of OSA. In addition to increased overall crash risk, one study also found that subjects with obstructive sleep apnoea syndrome had an odds ratio of 5.2 for having multiple crashes [58].

Case control studies may be influenced by a variety of biases that can result in false positive results. However a large prospective cohort study supports the association between OSA and crash risk found in the case control studies [62]. This study was performed in a general population of employed adults. The odds ratio for having an accident was 4.2 in men with mild OSA (RDI 5–15) and 3.4 for those

Table 1 OSA and Road Crash Risk.

Author	Year	Study Design	Population	Crash Risk
Findley	1988	Case-control	Sleep clinic	7.0 RR
Aldrich	1989	Case-control	Sleep clinic	1.0 OR
Wu	1996	Cross-sectional	Sleep clinic	3.0 OR
Young	1997	Prospective cohort	General population	4.2 OR
Barbe	1998	Case-control	Sleep clinic	2.3 OR
Teran-Santos	1999	Case-control	Drivers from traffic accidents	6.3 OR
Horstmann	2000	Case-control	Sleep clinic	8.7 RR
George	2001	Case-control	Sleep clinic	3.0 RR
Howard	2004	Cross-sectional	Professional drivers	1.6 OR

RR = rate ratio and OR = odds ratio

with moderate to severe disease (RDI > 15), so again no relationship was found between severity of OSA and crash risk [62]. Although there was no increased risk of having crashes in women with OSA, there was a marked increased risk of having multiple accidents in both women and men with OSA.

A few studies have not identified a relationship between road accident risk and OSA. Aldrich found an increased risk of sleep related accidents in patients with OSA, but did not find an increased overall accident risk [63]. Both accidents and sleep related accidents were evaluated by self-report, hence reporter bias may have influenced the results, particularly for sleep related accidents.

Treatment of OSA with nasal CPAP appears to reduce crash risk. Several studies have assessed crash risk before and after implementation of nasal CPAP therapy and found a reduction in crash frequency of between 31 % and 100 % [15, 16, 64]. These were all uncontrolled studies and so are open to the possibility of a placebo effect or other factors apart from CPAP accounting for some of the result. George performed a controlled study in 210 patients with moderate to severe OSA and matched control subjects [65]. Patients had a threefold increased crash risk compared to the control subjects, prior to treatment. During a three-year treatment period the crash rate in treated patients fell to the same level as control subjects. In a subset of patients (n = 27) who remained untreated the crash rate remained elevated and unchanged.

Case-controlled studies indicate that OSA patients as well as unselected subjects with OSA from general populations have an increased risk of having a road crash. They are also more likely to have multiple crashes. Whilst some studies have found a relationship between severity of OSA and crash risk, this is not a universal finding. Similarly, many of these studies did not find any significant relationship between sleepiness and crash risk in subjects with OSA, but a few studies have

found a relationship. Treatment of OSA with nasal CPAP appears to reduce crash risk, but the data supporting this finding is limited. Ethically it would be difficult, however, to perform a randomized placebo controlled trial addressing this issue. One factor that may contribute to the increased crash risk in OSA patients is the concomitant effect of drugs on their daytime functioning. The following sections will discuss the prevalence of drug use amongst this population of patients, and the effects on both nocturnal symptoms and daytime functioning.

Drug use in sleep apnea

Drugs use may occur coincidentally with sleep apnea, but drugs may also be used to treat associated medical conditions or to treat the direct effects of sleep apnea. Sleep apnea is related to several other medical conditions, including hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease and stroke [66–70]. People with sleep apnea may also present with depression [71]. Hence there is an increased likelihood that people with OSA will be on prescription medications for these conditions. For instance, in a study of over 200 000 patients receiving medical insurance, medical records of prescriptions for anti-depressant and anti-hypertensive medications was examined. Of all the patients, 1.29% were OSA sufferers, which was slightly lower than the population average. In this sample, the percentage of patients receiving prescriptions for hypertensive medication and antidepressants increased significantly with age. The authors concluded that the likelihood of having a diagnosis of OSA increases when either hypertensive or antidepressant medication are prescribed [72].

Given that sleep apnoea and the use of some drugs that impair driving are both common, it is likely that drug use and sleep apnoea will often co-exist. Insomnia in OSA patients may even lead to the prescription of sedatives and hypnotics (such as benzodiazepines, opioids and barbiturates). Alcohol and benzodiazepine abuse was identified in eight and three percent of sleep apnoea patients in a Swedish study [73]. This was similar to the frequency reported in the general population. In a large study of commercial vehicle drivers 4% reported using one or more of either benzodiazepines, narcotic analgesics and antihistamines [60], with over half of the drivers also found to have OSA. Alcohol use was also common.

The use of alcohol and psychotropic medications in people with sleep apnea is reasonably common. There is the potential for drugs to alter the severity of sleep apnea or exacerbate its neuropsychological sequelae and impair driving.

Drugs with adverse effects on breathing during sleep

Central nervous system depressant drugs can alter wakeful respiration if a sufficient quantity is administered. They may also influence breathing during sleep by altering upper airway tone, modifying chemoreceptor function, or altering the response to

stimuli (such as airway obstruction) during sleep. Opioids, hypnotics, sedatives and alcohol may compromise breathing during sleep in sleep apnea sufferers, potentially exacerbating daytime functional impairment including driving performance.

Alcohol

Alcohol is a socially accepted and widely used drug around the world. In low doses alcohol affects the main inhibitory (Gamma Aminobutyric Acid or GABA) and excitatory (glutamate, NMDA receptor) neurotransmitters in the CNS, facilitating inhibition and reducing excitation. During wakefulness, alcohol consumption can be associated with irregular breathing patterns and transient apneas; however, these respiratory depressant effects are generally mild [74, 75]. Nevertheless, while alcohol only has mild respiratory effects during the waking state, considerable literature now demonstrates that alcohol consumption prior to bedtime can precipitate sleep apnea or exacerbate pre-existing OSA. Alcohol depresses hypoglossal nerve activity, causing hypotonia of the pharyngeal dilator muscles [76, 77]. Alcohol also induces vasodilatation and swelling of the respiratory mucosa. Thus, regular intake of alcohol can induce OSA in a person with primary snoring [78, 79], and can also increase the number and duration of apneas during sleep in OSA patients [80, 81]. This can occur with modest amounts of alcohol [78, 80, 82]. The resultant fragmented sleep, changes in sleep architecture and potentially hypoxia can increase sleepiness and neurocognitive impairment [83, 84]. This may be particularly detrimental for individuals who already have sleep apnea.

Sedatives/Hypnotics

Benzodiazepines are one of the most widely used hypnotic agents. Like alcohol, the central nervous system pharmacological actions of benzodiazepines are mediated *via* an interaction with the gamma-aminobutyric acid (GABA)-BDZ receptor complex [85]. Benzodiazepines are generally a relatively mild respiratory depressant, and the effects on daytime breathing in normal subjects are negligible at recommended doses [86]. The impact of these drugs on respiration may be more important in sleep apnea patients, although there are conflicting study results.

Benzodiazepines may decrease upper airway muscle tone, which could increase the likelihood of upper airway collapse and alter the severity of OSA. A small but significant increase in duration of apneas and hypopneas, and lower nadir in arterial oxygen during NREM sleep was found in 12 patients with severe OSA following a dose of triazolam (0.25 mg) [87]. Oesophageal pressure measurements prior to apnea termination were also higher. This study concluded that triazolam increases arousal threshold to airway occlusion, resulting in modest increases in apnea duration and oxygen desaturation. Midazolam has also been found to produce greater oxygen desaturation during the sleep, with little effect on the frequency of apneas or hyponeas, supporting the concept that benzodiazepines increase the threshold for arousal from sleep resulting in longer respiratory events and greater oxygen

desaturation [88]. Similar effects have been demonstrated with non-benzodiazepine drugs. A single dose of Zolipdem (20 mg) produced trend level effects towards increased apnoeas, and significantly more oxygen desaturation compared to placebo and flurazepam (30 mg) in a study of 12 OSA patients [89].

Despite the concern that benzodiazepines may cause OSA or exacerbate existing OSA, some studies have found no effect of benzodiazepines on sleep apnea severity. Hoijer, et al. (1994) found no significant change in apnea severity or oxygen saturation in 14 OSA patients following an acute dose of nitrazepam (5 mg and 10 mg) compared to placebo [90]. Similarly, a study of 30 obese patients found no relationship between chronic benzodiazepine therapy and sleep apnea severity [91].

These studies suggest that benzodiazepines may have a small effect on OSA severity and the arousal threshold from sleep, resulting in greater oxygen desaturation at night. These effects are probably small, however, at clinically relevant doses and appear unlikely to have a significant effect on OSA severity in people on treatment. There may still be a detrimental effect from hyponotic drugs on daytime cognitive function, which could exacerbate the cognitive and driving performance impairment commonly found in OSA patients.

Narcotics/Opioids

Opioids are commonly used for acute and chronic pain management and occasionally prescribed for restless legs syndrome. Opioids have a significant respiratory depressant effect [92, 93] that is stronger than that of sedative-hypnotic drugs and ethanol. Respiratory suppression is mediated predominantly *via* their action on opioid receptors in the respiratory centres of the medulla and pons in the brain stem [94]. Decreased minute ventilation, and markedly reduced hypoxic and hypercapnic ventilatory responses occur in awake, healthy subjects in response to morphine, with a dose related effect [95]. Severe respiratory suppression, with post-operative respiratory arrests have been reported in some OSA patients prescribed opioid analgesics [96].

Following a single dose of hydromorphone hydrochloride in healthy subjects, both 2 mg and 4 mg doses decreased minute ventilation. However, no change was observed in measures of sleep apnea (frequency of apneas or hypopneas or oxygen saturation). Similarly, Shaw et al. (2005) found that a single dose of morphine (0.1 mg/kg) did not induce sleep apnea in healthy subjects [97].

There is, however, evidence of individuals developing sleep apnea following long-term opioid therapy, particularly central sleep apnea [98]. Thirty percent of people on a methadone program have been found to have central sleep apnea [99]. In a regression analysis, methadone concentration was related to the frequency of central apneas during sleep, but explained a small proportion of the variance [100]. A recent study of 120 people found an average increase of more than 30% in sleep apnea severity in those with chronic opioid use, predominantly due to central apneas [98]. Average oxygen saturation at night was also reduced in the opioid users. Although central apnea may be induced by opioids at clinically relevant doses,

there does not appear to be any effect from chronic opioid use on the severity of obstructive apnea [98, 100]. The impact of these changes in sleep apnea severity on daytime function and driving remains unclear, although those using opioids are more likely to have excessive sleepiness [100].

Drugs with beneficial influences on sleep apnea

Some pharmacological agents have been used for the treatment of OSA; however, none to date have been completely successful. No drug is presently indicated specifically for treating the underlying pathophysiology of OSA anywhere in the world. There are, however, many clinical trials currently underway testing the effectiveness of these treatments.

Antidepressants

Antidepressant drugs can indirectly reduce apneic events in OSA by altering sleep architecture. In most OSA cases, most events occur during rapid eye movement (REM) sleep. Antidepressant agents decrease or nearly eliminate REM sleep, and therefore may benefit patients who experience most apnea events during REM sleep [11].

Antidepressants may also stimulate upper airway motor neurons and potentially reduce airway collapse by inhibiting the reuptake of norepinephrine, dopamine, and serotonin at nerve terminals [11]. Mirtazapine appears to have beneficial effects upon multiple aspects of OSA pathophysiology. Mirtazapine has been shown to reduce the apnea index during NREM sleep by more than 50% ($p < 0.0001$) and during REM sleep by 60% ($p < 0.0001$) in rats [101]. In association with this apnoea suppression, inspiratory minute ventilation increased during all wake/sleep states ($p < 0.001$ for each state). In humans studies, mirtazapine directly increases upper airway tone [102], increases respiratory drive (Carley, 1999), and has been associated with an approximately 50% reduction in AHI [103]. However, in general, trials of antidepressants in humans have been extremely small in size and the effects upon the OSA severity (Apnoea-Hypopnoea Index AHI) have been modest. Further study of such drugs are warranted to determine whether improvements in sleep apnea severity from anti-depressants result in clinically meaningful improvements in daytime function and driving performance.

Stimulants

Modafinil was released in 1998 as a non-amphetamine treatment option for narcolepsy, and the associated excessive daytime sleepiness. More recently, several studies have examined the effectiveness of modafinil for the treatment of persistent sleepiness in OSA. Placebo-controlled studies of modafinil in a small number of

patients (n = 6 and n = 26) demonstrated a reduction in daytime sleepiness in people with OSA who had residual sleepiness despite treatment with CPAP [104, 105]. In a large, randomised, placebo-controlled, double-blind multi-centre trial, 157 OSA patients were given an oral daily dose of 400 mg modafinil *versus* placebo for four weeks [106]. Significant improvements in subjective and objective sleepiness, and psychomotor performance were demonstrated, with no subsequent change in CPAP compliance. Similarly, in a second multi-centre trial of 323 OSA patients, 200 mg and 400 mg daily doses of modafinil significantly improved subjective and objective daytime symptoms relative to placebo, and baseline [107]. Modafinil does not appear to impact on sleep architecture [108], and may also improve sleep latency times and quality of life measures [106]. Overall, modafinil seems to be an effective treatment for OSA patients with persistent excessive sleepiness despite treatment with CPAP therapy. It should be used as an adjunctive, rather than stand alone therapy, given that it will not prevent the cardiovascular sequelae and hypoxaemia that occur with sleep apnea.

Treatment of heart failure with central sleep apnea

Drug treatments for heart failure may have a beneficial effect on central sleep apnea and sleepiness associated with this condition. Cardio-selective β-blockers improve function and survival in patients with heart failure, with a recent study also evaluating their effect on the presence of central apnea [109]. In patients with moderate to severe heart failure the frequency of central apneas was reduced by more than 50 % in those on β-blockers, with a similar improvement in sleepiness. Other treatments for heart failure, such as angiotensin converting enzyme inhibitors, may also improve central sleep apnea and potentially the sleepiness associated with it.

Effects of different drug classes on daytime sleepiness, functioning and driving in sleep apnea

There is a paucity of studies examining the combined effect of sleep apnea and different drug classes on daytime sleepiness, psychomotor function and driving performance. Nevertheless, given that sleep apnea and many psychoactive drugs have detrimental effects on these functions, it seems likely that some drugs will exacerbate daytime impairment in sleep apnea sufferers. Some inferences can be drawn from studies evaluating the combined effects of inadequate sleep and alcohol intake, which have shown at least an additive effect on driving performance impairment [110, 111]. Other specific instances where drugs are likely to interact with sleep apnea are discussed below and, although not an exhaustive list, represent instances where this may commonly occur.

Sleep apnea increases road crash risk by increasing sleepiness and impairing neuropsychological function as a consequence of sleep fragmentation and recurrent tissue hypoxia. Drowsiness and sleepiness can stem from a number of factors, including: extended periods of wakefulness or inadequate sleep on a single day or on a chronic basis; circadian rhythm or time of day effects, which are important influences in shift work; task related effects, such as the duration and monotony of a task; medical disorders such as sleep apnea, insomnia and narcolepsy; and drugs, including benzodiazepines, alcohol, cannabis, opiates and antihistamines. Individually these factors have been shown to impair cognitive and or driving performance and increase crash risk. Since many drugs can cause daytime sleepiness and cognitive impairment that may be similar to the effects of sleep apnea, it is likely that the interaction of both sleep apnea and drug use may increase crash risk more than either factor alone. The evidence supporting this to date is limited, predominantly because of a paucity of studies.

Alcohol

When underlying sleepiness is mixed with a sedative substance such as alcohol, the impairments to neurobehavioral function, attention, and vigilance may be exacerbated [110, 112, 113]. This results in decreased alertness, reaction time and psychomotor deficits, with important implications for tasks such as driving [114, 115]. Even low BACs of 0.05g/dL can significantly impair driving performance and neurocognitive function in healthy individuals [114, 116–119]. There is a reduced ability to maintain alertness and attention, with increased impulsivity and errors [114, 116, 118, 120] and increased road crash risk [121].

OSA patients are effectively sleep deprived as a result of sleep fragmentation caused by apnea, in addition to the effects of hypoxia. Indeed, sleep apnea results in similar performance decrements to sleep deprivation. It is likely that an additive effect on performance impairment would result from the combination of sleep apnea and alcohol intake, even at low alcohol levels [110, 111]. Some idea of the likely combined effect of sleep apnea and alcohol can be gleaned from studies evaluating the interaction of sleep deprivation and alcohol on driving and performance. A number of studies have shown that the combination of sleep restriction and low doses of alcohol result in a greater decrement in driving performance than alcohol or sleep deprivation alone [110, 112, 113]. A recent study aimed to determine the combined effects of sleep restriction (4 h) and low-dose alcohol (at two levels: 0.025 g/dL and 0.035 g/dL) on a 70 minute driving simulator performance in the mid-afternoon. Steering deviation increased significantly when sleep restriction was combined with the higher dose alcohol. This combination also resulted in a significant increase in alpha/theta EEG activity throughout the drive, a measure of increased sleepiness.

Extended wakefulness of 18–21 hours without prior sleep restriction has also been shown to severely impair driving simulated driving performance when com-

bined with low dose alcohol (0.03%) [111]. Both variation in speed and lane position were impaired with this combination, with performance worse than that at an alcohol level of 0.05%, a level known to increase crash risk. These studies indicate that combining low-dose alcohol with moderate sleep deprivation results in significant decrements to some simulated driving performance parameters at a level that may increase crash risk. Evaluation of crash data also suggests that there is a marked increased risk of death (RR 6.8) when both sleepiness and alcohol are contributory factors, compared to either factor alone [51]. The effect of alcohol on crash risk may be partly mediated by sleepiness [122]. The addition of alcohol to sleepiness also appears to impair perception of performance, particularly in men [110, 113, 123]. This means that sleepy subjects may fail to realise when their performance is impaired. These studies highlight the potential risks of driving after consumption of alcohol, even at low levels when combined with sleepiness.

Whilst the studies outlined above were performed in healthy sleep deprived subjects, it seems likely that similar effects would occur when people with sleepiness as a result of sleep apnea also consume alcohol. The brain of OSA patients, already impaired as a result of the effects of sleep fragmentation and hypoxia, would be further susceptible to the effects of alcohol. This would be likely to exacerbate the pre-existing neurocognitive and driving performance deficits in OSA patients, although laboratory studies have not specifically addressed this question to date. As demonstrated in the sleep deprivation studies, severe performance impairment and altered perception of performance may occur even at low alcohol doses. One cross sectional study evaluated the relationship between crash risk and several potential causative factors in a group of over 3000 commercial vehicle drivers [60]. The risk of having a crash was increased by 30% in drivers with symptoms of sleep apnea syndrome, with an even higher risk of having a single vehicle crash (a marker of sleep related crashes). This was adjusted for established risk factors, including alcohol intake, which itself was associated with a nine percent increase in crash risk for every 1.8 standard drinks consumed per day. This data suggests that alcohol use in combination with sleep apnea results in a higher crash risk than either alone. In a multivariate model from the same study, sleep apnea did not remain a significant predictor of crashes, although sleepiness did predict crashes. This suggests that the increased crash risk associated with sleep apnea was mediated by sleepiness, although this has not been confirmed in some other studies.

Given that sleepiness, induced by sleep deprivation, in combination with even low levels of alcohol can result in severe driving performance impairment, it seems likely the combined effect of alcohol intake and cognitive deficits associated with sleep apnea would also result in significantly impaired driving. There is some limited epidemiological evidence to suggest that this combination would result in a higher crash risk than either alone. In particular, this interaction would be important in people with undiagnosed sleep apnea, those who remain untreated (as often occurs in mild to moderate disease) and even in those on treatment who may have residual cognitive deficits. This warrants further investigation in order to determine safe alcohol guidelines in those with OSA, particularly with regards to driving.

Cannabis

The psychoactive component of cannabis, Delta-9-tetrahydrocannabinol (THC), stimulates the dopamine pathway, known to be associated with reward systems in the brain [124]. Two endogenous cannabinoid receptors have been identified; CB1 primarily in the brain, and CB2 found in peripheral tissues [125, 126]. Very few receptors are found in the brain stem, which may be the reason why high levels of THC do not suppress respiration [124]. Cannabis can cause sleepiness and sedation, however, particularly at high doses. This has been demonstrated in normal subjects, but has not been evaluated in people with sleep apnea [127, 128].

Cannabis is the most common psychoactive drug associated with increased road crash risk other than alcohol [129]. There is some evidence that cannabis-related accident risk may be associated with driver sleepiness. In a case controlled study in New Zealand, the association between acute cannabis use and car crash injury was significant after controlling for age, gender, time of day and ethnicity [130]. However, when controlling for other risky driving variables, including sleepiness, this association was non-significant. The combined effect of sleep apnea and cannabis on crash risk has not been evaluated. Whilst there is no current evidence of the effect of acute cannabis use on sleepiness in OSA patients, it is likely that cannabis would increase daytime sleepiness in these patients with the potential to increase crash risk.

Benzodiazepines

Many of the known cognitive effects of benzodiazepines overlap with those induced by sleep apnea. Benzodiazepines induce sleepiness, with associated impairment of psychomotor function. Short and intermediate acting benzodiazepines increase sleepiness and slow reaction time [131–133]. Higher cortical functions, such as logical reasoning, attention and the ability to multi-task are also impaired [133, 134]. Even ultra-short acting forms may slow reaction time for up to three hours, with the effects of intermediate acting drugs lasting for more than six hours [134]. Regular use of benzodiazepines for anxiety impairs driving performance, with increased variation in lateral lane position associated with sleepiness [135]. There is also evidence of dissociation between objective performance impairment (slowing of reaction time) and subjective symptoms following benzodiazepine ingestion in the elderly [132]. Poor perception of impairment following benzodiazepine use may lead to people driving because they feel normal, even though functional impairment is present. It is likely that benzodiazepine use would exacerbate sleepiness and cognitive impairment in sleep apnea sufferers, although this has not been specifically studied in the laboratory. In a large cross-sectional study of drivers, benzodiazepine use was associated with a two-fold increase in crash risk [60]. Those with symptoms of sleep apnea syndrome also had an increased crash risk, although the combined effect of benzodiazepine use and sleep apnea was not reported. Similarly,

benzodiazepine use was increased in OSA patients compared to controls, with the OSA patients also having a higher crash rate [58].

These studies raise the possibility that sleep apnea and benzodiazepine use may have a combined effect on sleepiness and road crash risk, but this remains to be confirmed. Whilst treatment of sleep apnea may return daytime function to normal, this is not always the case. Hence, it would be appropriate to avoid use of hypnotics in people with sleep apnea, particularly if they are driving. It may be safe to use hypnotics at night and then drive the following day [136, 137], However, this has not been specifically studied in sleep apnea subjects.

Opioids

Opioids may exacerbate cognitive deficits in people with sleep apnea by inducing central sleep apnea or by direct central effects on cognitive function. Chronic opioid use is related to excessive sleepiness [100]. In this controlled trial, eight percent of those on a methadone program had excessive sleepiness, whilst no control subjects had excessive sleepiness. This may have been partially due to the increase in sleep apnea in these subjects. Slower reaction times, lapses in attention and microsleeps have been identified in people following anaesthetics that include opioids [138]. Patients with cancer on high dose morphine for pain relief often experience severe daytime sleepiness, which may limit the dose used for analgesia [139]. The degree of sleepiness is lower if the opiate dosage can be reduced [140] and central stimulants may also reduce the degree of sleepiness [141]. Whilst it has not been specifically studied, it appears likely that opioid usage would exacerbate sleepiness in patients with sleep apnea and should be used with caution. Opiate use was associated with a more than two-fold increased risk of crashes in a commercial vehicle driver study, with sleepiness and opiate use both contributing to crash risk in a multivariate model [60]. Sleep apnea syndrome also increased crash risk in the same study, but it was not included in the model, suggesting its effect was mediated by sleepiness.

Antihistamines

Histamine (H 1 receptor) antagonists are commonly used for allergic rhinitis and other allergic reactions. They induce sleepiness and impairment on psychomotor tests [142], although to a lesser extent with second generation agents [143]. Tolerance may develop to the sedative side effects with regular use of antihistamines, although it is unclear how this translates to the clinical setting, where usage is often sporadic [144]. Allergic rhinitis itself may cause sleep disruption and daytime sleepiness [145] and in patients with OSA nasal obstruction may make it difficult to tolerate treatment with nasal CPAP. Hence, treatment of nasal obstruction has the potential to improve sleep quality and daytime sleepiness. This has been demon-

strated with nasal corticosteroids, but not with antihistamines [145]. The combined effects of anti-histamines and sleep apnea on sleepiness and performance have not been studied in the laboratory. Antihistamine use has been associated with a three-fold increased risk of road crashes, independent of the effects of sleepiness [60]. Sleep apnea syndrome was associated with a 30 % increase in crash risk in the same study, although this effect appeared to be mediated by sleepiness. These findings raise the possibility that sleep apnea and anti-histamine use may have at least a combined effect on crash risk, although this remains to be confirmed.

Other drugs

Although β-blockers may have a beneficial role in treatment of central apnoea and sleepiness related to heart failure, they may also cause daytime sleepiness [133]. In a single dose study, atenolol slowed motor performance and increased sleepiness [133]. Daytime sleepiness has also been reported in people on long term treatment with β-blockers, with resolution after ceasing treatment [146]. Anti-psychotic drugs may also induce sleepiness, with associated slowing on electro-encephalography [147]. No trials have been conducted to evaluate whether these medications exacerbate sleepiness in sleep apnea patients. However, given that their usage is common, clinicians need to be aware of the potential of exacerbating sleepiness and crash risk in this group.

Conclusion

Sleep apnea, sleepiness from other causes, alcohol and other psychoactive drugs all impair driving performance and increase road crash risk. There is growing evidence that alcohol and sleepiness induced by sleep deprivation results in severely impaired driving performance, impaired perception of performance and increased risk of fatal crashes. It is likely that alcohol use in sleep apnea would have a similar effect. The evidence that this is the case is limited, but suggests that sleep apnea and alcohol use at least have independent effects on crash risk. This is similar for other drugs, including opiates, benzodiazepines and anti-histamines. Some drugs, such as alcohol and opiates may also increase the severity of sleep apnea itself. One of the difficulties in assessing the combined impact of drugs and sleep apnea on crash risk, particularly fatal crashes, is that drivers are not usually asked about sleep apnea symptoms. Sleepiness is also difficult to measure, particularly after the crash, and not routinely assessed. At present, those with untreated sleep apnea should avoid alcohol and psychotropic drugs that increase crash risk. They should also be used with caution in those on treatment, as residual sleepiness may be present in people with sleep apnea on treatment. Further research is required to define the impact of these drugs on driving performance in both treated and untreated sleep apnea.

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Drugs, Driving and Traffic Safety
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Drugs, driving and traffic safety in shift workers

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Abstract

Shift work and other irregular working schedules are common in modern society, but may also lead to disruptions in the regulation of sleep and wakefulness. Intolerance to shift work may lead to Shift Work Sleep Disorder (SWSD), primarily characterized by insomnia and excessive sleepiness.

The effects of shift work on driving ability and traffic safety have been demonstrated in a number of epidemiological and driving simulator studies. The main consequences of shift work are fewer hours of sleep, higher levels of sleepiness, and falling asleep while driving. Consequently, increased traffic accident risk has been reported relative to daytime workers (odds ratio 1.14 to 2.3). Different strategies are available to combat driver fatigue and accidents in shift workers. Alertness can be improved by prophylactic napping or by using stimulant drugs such as modafinil, a compound specifically targeting SWSD. Another way to combat the negative effects of shift work is manipulating the circadian system by administering melatonin and bright light. Future research should identify the factors leading to SWSD and impaired driving, so that optimal strategies can be developed.

Introduction

Before the introduction of electrical light, humans largely adapted their daily activities to the natural light-dark cycle. When modern technology enabled the production of artificial light, it became possible to change this rhythm and work during the dark part of the day. After the industrial revolution, factory managers wanted to make optimal use of their machinery by designing work schedules that enabled continuous around-the-clock production, leading to an increase in the number of people working in the evening and night. Later, this trend progressed to other areas

such as the service industry. All these developments contributed to our 24-hour society with its numerous benefits. However, there are also a number of negative side effects.

Humans have an endogenous biological rhythm, set by light exposure, which has a limited ability to adapt to artificial sleep-wake schedules. Evidence for the potentially hazardous effects of irregular working hours has been found in recent years, showing that inability to adapt to alternative or irregular work schedules may result in insomnia, drowsiness, cognitive impairments [1], and even serious illnesses [2]. Furthermore, a decrease in occupational performance and an increase in accident risk, both at work and on the road, may be the result.

In this chapter, the effects of irregular working hours on traffic safety are discussed, as well as empirical evidence on road traffic accidents and driving simulator studies in shift workers.

Shift work and flexible working hours

About 15–40 % [3–5] of the working population in industrialized countries perform their work at times at which others are asleep or enjoy leisure time. These workers are usually referred to as shift workers. Common examples are factory workers, police officers, and medical personnel. Yet, the concept of shift work is quite vague, which is reflected by the fact that there is no consensus over a proper definition. Although several definitions are in use, most agree on one criterion: all or part of the duties are performed outside standard working hours [6, 7]. Usually, working days commencing after 6.00–8.00 a.m. and ending before 6.00–7.00 p.m., with a maximum of 8 hours per day and approximately 40 hours per week, are considered to be standard [8, 9]. In addition, standard work is performed during a continuous on-duty period, except for breaks [8].

There is a wide variation of systems in use for the organization of shift work. Each can be described according to a number of characteristics:

- *Shift type:* morning shift (MS), afternoon shift (AS), evening shift (ES) or night shift (NS)
- *Start and ending times of each shift type*
- *Duration of shift*
- *Number of consecutive shifts*
- *Shift schedule:*
  - Fixed schedules: similar start and end time over a prolonged period of time
  - Rotating schedules: shift type changes after a certain number of days characterized by:
    - direction of rotation: forward (clockwise) or backward (counterclockwise)
    - speed of rotation

A distinction can be made between “conventional” shift work, in which people work a substantial part of the working week outside normal daytime hours, and flexible

working hours, which include early starts and late finishes, overtime, compressed workweeks, and other irregular schedules. The latter has its own definition: "*Flexible working hours involve a continuous choice on behalf of employers, employees or both, regarding the amount (chronometry) and the temporal distribution (chronology) of working hours*"[10]. In other words, whereas "conventional" shift work is usually organized according to strict schedules, an important feature of flexible working hours is that they are not.

One commonality between conventional shift work and flexible working hours is that people work during "unnatural" times. Therefore, another definition seems more appropriate: "*Shift work refers to work patterns that extend beyond the conventional 8-hour work day and that potentially disrupt workers' normal biological and/or social diurnal rhythms*" [11].

Shift work sleep disorder

In a proportion of workers, shift work leads to a circadian rhythm disorder called Shift Work Sleep Disorder (SWSD), also known as "shift lag". Following the *International Classification of Sleep Disorders*, the minimal diagnostic criteria for SWSD are insomnia and excessive sleepiness which are associated with a work period overlapping the normal sleep period [12]. Since there is no clear definition of shift work, it is also difficult to estimate an accurate prevalence of SWSD. This is also hampered by the so-called "healthy worker effect": intolerance to shift work compels workers to adopt other types of occupation leading to the "survival" of the healthiest shift workers. The American Academy of Sleep Medicine estimates a prevalence of SWSD of two to five percent in the total population [12]. These figures exclude early morning workers, suggesting that the actual prevalence may be higher. Drake et al. [13] assessed the differential prevalence of SWSD by comparing with daytime workers. They found a prevalence of 14.1 percent in night workers and 8.1 percent in rotating workers corresponding with an overall prevalence of SWSD of 10 percent in the shift worker population.

A further issue is that individuals may be diagnosed with SWSD according to the two previously mentioned criteria, but the question that remains is: Where is the boundary between a normal response to night or shift work and a pathological response, i.e. a true diagnosable disorder [14]?

The symptoms related to SWSD arise from disruptions in the regulation of the sleep-wake cycle. Circadian and homeostatic processes are of importance in this regulation. The circadian oscillator or body master clock, located in the suprachiasmatic nucleus (SCN) in the hypothalamus, is responsible for generating cycles of about 24 hours. The clock is "set" each day by light input from the retina relayed to the SCN. After the onset of darkness, the SCN controls the secretion of melatonin by the pineal gland, which in turn initiates sleep. Thus, the circadian process enables sleep during the night and wakefulness during the day. The homeostatic process corresponds to a "need for sleep" that increases during wakefulness in a progressive

manner. Both processes may also predict alertness and performance [15]. Irregular working hours lead to disruptions in these processes. Especially in rotational shift work, workers constantly need to adjust to different sleep-wake times. The same holds true for night work. Theoretically, full adaptation to continuous night work is possible, yet slow: estimated at 1 hour per day. In real-life situations, workers often revert to a normal day-night schedule during weekends and holidays. In addition, exposure to light in the morning produces a phase shift that counteracts the process of adaptation [16]. Apart from the biological factors, environmental factors such as noise and light, and social factors, e.g. deliveries, phone calls and family members' demands, may compromise sleep during the day.

Insomnia amongst shift workers results in a decrease in total sleep length and quality. Night shift workers regularly report sleepiness and lack of alertness and vigilance while working, all of which impair performance [12]. Additionally, the energy loss and fatigue will interfere with normal social functioning and may have harmful psychological effects. This emphasizes the need of adequate management of the disorder, including early diagnosis and recognition of its severity.

Traffic safety in shift workers

A study by the AAA Foundation for Traffic Safety showed that after alcohol consumption, drowsy driving was the most important cause of car crashes [17]. Work schedules were significantly associated with sleep-related crashes. Anyone not working regular day shifts was twice as likely to become involved in a sleep-related crash as opposed to a non-sleep-related crash. In night shift workers, the risk was almost 6 times higher when compared with non-sleep-related crashes, and over 13 times higher when compared with non-crash controls [17]. Studies focusing on shift workers and the factors found to be involved in drowsy driving and shift work are discussed in the next sections.

Commuting shift workers

Epidemiological studies

Several studies suggest that road traffic accidents are especially common in shift workers at their trip to and from work. A survey by Gold et al. [18] showed that nurses on rotating schedules had an odds ratio (OR) of 1.14 to report a car accident and OR of 2.63 to report a near-miss accident, as compared to day or evening nurses. In night nurses, an OR of 2.24 for a car accident and an OR of 1.92 for a near-miss accident were found. Nodding off when traveling to or from work was reported by 49 percent (OR = 3.62) of night nurses and 51 percent (OR = 3.92) of rotators.

Reduction in sleep duration at workdays may be an explanation for the increased accident risk [19]. A different study in nurses showed that prior to evening shifts,

nurses had more sleep than prior to night or morning shifts. Near-miss accidents and drowsiness were mainly associated with the night shift. Furthermore, struggle to stay awake at work, followed by exhaustion and the number of consecutive shifts, were significant predictors of drowsiness and near-miss accidents on the way home. Nurses did not report significantly longer working hours. Therefore, it seems likely that the rotating shift schedule itself produced sleep loss [19].

Another study did report that extended shifts were a contributing factor in drowsy driving and related vehicle accidents [20]. Work hours in 2737 residents in US medical schools (interns) and the incidence of motor vehicle crashes and near-miss incidents after an extended work shift (>24 hours) were compared to those observed after a normal shift [20]. The risk of crashes (OR=2.3) or near-miss incidents (OR=5.9) was significantly greater after an extended shift than after a non-extended shift. Moreover, for each extended work shift scheduled per month, the overall monthly risk of a crash was increased by 9.1 percent while the risk of a crash while driving home from work was increased by 16.2 percent. In addition, odds ratios for falling asleep behind the wheel corresponded significantly with the monthly number of extended work shifts.

Rogers et al. [21] found that a sleep duration before work of less than 6 hours, the night shift, and travelling times of more than 35 minutes, were associated with sleepiness and driving impairment. Di Milia [22] also reported that sleepiness after long-distance driving following night work was significantly higher in shift workers (n=180) when compared to non-shift workers (n=1375) in Australia. Severe sleepiness was reported by 19 percent of shift workers *versus* 1 percent of non-shift workers.

A case-control study showed that each hour of sleep reduction below 7 hours resulted in a significantly higher odds ratio of having a sleep-related traffic accident [23]. Furthermore, working a night shift, rotating shifts, and working 60 or more hours per week were associated with sleep-related motor vehicle crashes.

Epidemiological evidence confirms that shift workers experience high levels of sleepiness associated with increased accident risk. The most important findings are summarized in box 1.

Major findings from epidemiological studies in commuting shift workers:

- high prevalence of sleepiness and nodding off when driving home after night shifts and rotating shifts
- struggle to stay awake at work, exhaustion and number of consecutive shifts can predict drowsiness and near miss accidents after shift work
- extended shifts increase the risk of crashes and near-miss incidents
- the risk of falling asleep behind the wheel increases with the number of extended shifts per month
- long driving distance after shift work is related to severe sleepiness
- sleep durations below 6–7 hours are associated with sleep related crashes

Box 1

Simulated driving performance studies

Driving performance of shift workers has been examined in five driving simulator studies.

Åkerstedt et al. [24] compared driving performance after a night of normal sleep and after a night shift in the morning (7.00–7.30 a.m.) in male and female shift workers (n = 10). The night shift led to an increase in blink duration and subjective sleepiness and to impairments in driving ability. After night work, there was a significant increase in incidents (two wheels outside the lane markings), reduced time to the next accident (four wheels outside the lane markings), and increased weaving of the car compared to driving after a night sleep. A second study [25] investigated the effects of different shift types (morning, afternoon and night shift) and shift systems (slow backward *versus* fast forward rotating schedule) on simulated driving in male and female shift workers (n = 36). A 25-minute drive was performed after each shift (5.30 a.m., 10.00 p.m., 2.00 p.m.). Weaving of the car increased after the night shift, as compared to the afternoon shift, and increased during the drive. However, no differences in weaving were found between the slow and fast rotating shift systems. Neither the shift type nor the shift system had an influence on the number of accidents, i.e. the car leaving the road or hitting another vehicle. However, significantly higher sleepiness levels were reported in the slow-backward rotating group. In addition, after the morning and night shift, higher levels of sleepiness were reported than after the afternoon shift.

Smith-Coggins et al. [26] examined physicians and nurses (n = 49) working three consecutive night shifts in an emergency department. The effects of napping during the night shift on driving performance were examined in the morning (8.00 a.m.) after the second and third shift during a 40-minute drive. In addition, videotapes of the subjects' faces during the drive were analyzed for signs of alertness. During the last night shift, subjects in the nap-group were given the opportunity to sleep for 40 minutes between 3.00 a.m. and 4.00 a.m. No differences were found on overall driving performance. Dangerous driving, in which the car leaves the road or collides with another vehicle, occurred relatively often in both groups: approximately 8 percent of the total driving time. Driver alertness data suggested that a nap improved alertness. However, the data from this study may be influenced by individual characteristics of the drivers in the napping group. Studies often show that a few individuals often account for a relatively large proportion of accidents and incidents. For example, large individual variation in driving time until the first crash occurred was found in non-shift-working drivers the afternoon after a night of sleep restriction [27]. The presence of a group of subjects who are more sensitive than others makes it difficult to interpret the data on a group level. The impact of individual differences on sleepiness and driving performance was addressed in a fourth simulator study in shift workers [28].

An interesting finding regarding individual differences was derived from a fifth driving simulator study in medical residents (12 male; 7 female) [29]. The effects on driving and sleepiness were assessed after a night on-call and a night off-call. The results showed a significant difference between males and females: male resi-

dents drove significantly poorer after a night on-call as expressed by lane drifting and crash frequency. No overall differences between off-call and on-call were found on driving. During a night on-call, self-reported total sleep time was decreased and sleepiness was significantly greater. In addition, sleepiness was greater after the driving test as compared to pre-drive. It is likely that the difference between men and women was caused by women's ability to cope with sleep loss and maintain alertness. Because no difference was found in the off-call condition, risky behaviors in men are unlikely to lead to the difference in driving ability.

The major findings derived from simulator studies are summarized in box 2. It has to be noted that, although simulator studies aim to reflect real life situations, assessing driving performance in a simulator has limitations. Driving simulators may enhance sleepiness [24]: because subjects know there is no real risk, they may be less stimulated, less willing to exert effort and fall asleep sooner. In addition, dim light conditions in a simulator may also increase sleepiness. The accident risk derived from these studies may therefore be larger than in real-life situations. In addition, as different aspects and different shift worker populations in different shift systems were assessed, the comparability is limited. Future research should aim to examine uniform groups of shift workers, preferably in on-the-road driving studies in normal traffic.

Major findings from driving simulator studies in shift workers:
- night shifts and early morning shifts lead to increases in lane drifting, accident risk and subjective sleepiness scores
- afternoon shifts have few negative consequences
- napping may improve alertness
- subjective sleepiness levels are predictive of accident propensity
- few drivers account for relatively large numbers of accidents
- personality traits are likely to be involved in the adaption to shift work
- males seem to be more at risk than females

Box 2

Occupational drivers

In the transportation industry, the effects of disrupted sleep-wake schedules may have serious consequences. Truck drivers often work irregular hours including night work, and often spend long hours behind the wheel. Taking into account that a fully loaded truck may weigh over 45,000 kg, truck crashes regularly lead to serious injuries or death. These and other occupational drivers such as bus and taxi drivers face additional challenges when confronted with irregular working hours. Especially the combination of circadian disruptions and long driving hours may lead to drowsiness and increased accident risk.

A study by the United States National Transportation Safety Board (NTSB) revealed that 31 percent of all fatal commercial truck crashes were attributable to

fatigue. This was the most likely cause of crashes, preceding the use of alcohol and drugs [30]. However, large differences in the percentages of accidents attributed to fatigue are seen, probably caused by underestimation of the role of sleepiness in police reports [31].

Another study by the NTSB showed that drivers with irregular working hours were more often (67 percent) involved in fatigue-related accidents than drivers working regular hours (38 percent). The duration of the sleep period, the total amount of sleep in the preceding 24 hours and split sleep patterns were most predictive for fatigue-related crashes [32]. This study confirms that sleep deprivation plays an important role: truck drivers who were involved in a fatigue-related accident had on average 2.5 hours less sleep than drivers involved in other types of accidents.

Several studies support this finding. Sleep durations of 5–6 hours per night are often reported by drivers [33–35]. As many as 30 to 47 percent of commercial drivers reported falling asleep behind the wheel [36, 37]. The numbers differ depending on the driver population: a distinction between long and short haul driving is often made. Especially in long haul truck driving, i.e. long distance driving, which requires sustained attention, truck drivers are believed to be primarily at risk for accidents. Yet, short distance driving may also be influenced by sleep restriction. In a study in daytime short haul drivers, fatigue was reported by 38 percent of subjects at least once a week and 45 percent reported nodding off while driving in the preceding year. Factors associated with a higher frequency of experienced fatigue were long work hours, high subjective workload, and the proportion of cargo movements from customers to depots [38]. A study comparing long and short haul drivers showed that 40 percent of long haul and 21 percent of short haul drivers had problems maintaining alertness in 20 percent or more of their drives. Approximately 25 percent of long haul drivers reported having nodded off at least twice while driving, whereas about 8 percent of short haul drivers reported this. Two or more near-miss accidents within the last 3 months were reported by 10 percent of long haul drivers and approximately 4 percent of short haul drivers [39]. In bus drivers, similar results were found. For example, 60 percent of Brazilian interstate bus drivers who worked in shifts reported sleep-related complaints, and 16 percent reported dozing off while driving [40]. This suggests that commercial driving *per se* leads to increased sleepiness in large numbers of drivers.

Several studies in truck drivers established a correlation between excessive sleepiness and driving accidents [33, 34, 41].

Long daily work hours and extended time on the road increase the accident risk. This was demonstrated in a study in Sydney taxi drivers. While the majority (67 percent) worked long shifts, breaks were short and a negative correlation between total average break time and accident risk was observed [42]. Other studies examining the total driving time demonstrated that accident risk significantly increases after 4–6 hours of driving [43, 44] and that accident risk significantly increases to a three-fold risk in the eleventh hour of driving [44].

Overall, sleep-related crashes occur more frequently at night or in the early morning and in the early afternoon [45–47]. A study using EEG parameters sup-

ported this by demonstrating that sleep-like states while driving were predominantly present during the late night and early morning [35].

Personality traits and coping strategy are quite probably of high importance in driver fatigue. Moreno et al. [48] compared the sleep duration and frequency of truck drivers on fixed schedules with truck drivers on irregular working hours. The latter displayed a polyphasic sleep pattern with more sleep episodes that had a shorter duration, whereas the drivers on fixed schedules displayed a monophasic sleep pattern. It is suggested that the ability to fragment sleep may be an individual trait or a coping strategy, which manifests itself under certain circumstances, such as work pressure. On the other hand, another possibility might be that truck drivers' unhealthy lifestyle leads to sleep disturbances displayed by fragmented sleep. Still, similar to studies in commuting shift workers, commercial driver studies have shown that few drivers account for a large percentage of accidents [49].

Stress and high work demands also influence driving performance [36, 38]. To protect drivers from extreme working hours, most countries limit driving times by setting up driving and resting time regulations controlled by using tachograph discs to record driving times. However, commercial pressure sometimes leads transportation companies to force their drivers to break the driving time regulations. Cheating with tachograph discs is quite a common procedure, but solutions that are more creative are also regularly exerted. An example is the provision of false permission letters before sending drivers abroad. This way, a driver can "prove" to have had a day off, while in fact the driver has been working.

To keep up with high work demands, drivers often resort to stimulating substances to remain alert, although other reasons of abuse should not be excluded. Two Brazilian studies demonstrated that stimulant drug use was highly prevalent in truck drivers: 11.1 percent used stimulant drugs such as amphetamines and 77.1 percent of amphetamine users took them 6 times per week or more [33]. In the second study, 66 percent of drivers used amphetamines [50]. Two Australian surveys, as part of one study, support these findings: one in five and one in three truck drivers, respectively, reported stimulant use to fight fatigue. Frequent stimulant use was associated with breaking traffic rules, having extended working hours, and reporting higher sleepiness levels and falling asleep while driving [51].

The truck drivers in the Brazilian studies also reported high levels of alcohol use: 50.9 percent [33] and 91 percent [50]. About half of the drivers consumed alcohol at gas stations alongside the highways. In previous research, the combined effects of extended wakefulness and alcohol proved to have tremendous negative effects on simulator driving ability and on alertness, even when low, legal doses were consumed [52] and when the sleep restriction was moderate [53].

The final factor of importance is the prevalence of sleep disturbances in commercial drivers. A combined effect of shift work-related fatigue and sleep disorders may have serious results. Sleep-disordered breathing or sleep apnea are overrepresented in commercial drivers [41, 54] and the effects on traffic safety may be substantial. One study demonstrated a two-fold higher accident rate per mile in commercial drivers with sleep-disordered breathing as compared to healthy drivers [41].

The major findings on sleep-deprived commercial drivers and traffic safety are summarized in box 3.

Main factors associated with accident risk in commercial drivers:
- higher levels of daytime sleepiness
- poor sleep
- work schedules with long work hours and few breaks
- long total driving time
- circadian, i.e. time-of-day influences: higher risk at night/early morning and in afternoon
- high subjective job demands
- personality trait
- substance abuse
- sleep disorders

Box 3

Flexible working schedules

Most studies involving shift workers were not performed in flexible workers. Extreme cases, such as interns at medical hospitals working extended shifts of more than 24 hours, can seriously endanger traffic safety, but the effects of less pronounced flexible schedules are largely unknown. Due to the great variability of existing working hour arrangements, they have not been thoroughly investigated. Fact is that flexible work is becoming more common than in the past. One trend that may be of importance is early morning work, developed to avoid night work regulations and avoid traffic congestion in the morning. As mentioned previously, early morning shifts are related to sleep deprivation and thus may lead to an increase in road traffic accidents [55].

More research into various flexible working hour arrangements is necessary to examine possible accident risk in these groups of workers.

Countermeasures

Negative effects of shift work can be counteracted in several ways. Here, three methods will be discussed: (1) improving alertness by napping or the use of stimulants, (2) improving sleep by the administration of hypnotics, and (3) ways of preventing the circadian rhythm disorder.

Enhancing alertness

Napping

An effective way to combat fatigue is napping [56]. Different sleeping and napping strategies can be implemented to cope with nightly shift work in terms of length and timing [57]. The advantages of napping are outlined by Dhand et al. [58] highlighting the recuperative effects of daytime napping on alertness, performance and learning. In shift workers, napping prevents fatigue and increases performance [59–61].

A simulator study in shift workers showed that napping had a small but positive effect on driving [26]. More studies of this type are needed to determine the usefulness of napping in improving shift workers' driving ability.

Use of psychostimulants: modafinil

Several studies on the use of stimulant drugs show an improvement of alertness and cognitive performance [62]. Methylphenidate has shown to improve on-the-road driving performance in healthy volunteers [63] and patients with attention-deficit hyperactivity disorder (ADHD) [64]. However, the effects of stimulants on driving performance during or after shift work have not been studied. Although stimulant drugs such as amphetamines improve alertness, the risk of abuse and dependence makes amphetamines not a suitable approach in combating drowsy driving in shift workers [62].

Modafinil is a stimulant which is registered in the US and several European countries for the treatment of SWSD [65]. Its pharmacological actions are not yet fully understood but the dopaminergic and noradrenergic system are thought to be closely related to the wakefulness-provoking actions of modafinil [62, 65]. Several studies have been conducted on the effects of modafinil in dyssomnias. Studies specifically investigating the effects of modafinil in a SWSD population are scarce. Evidence of effectiveness of modafinil in SWSD is shown in studies where improvement of alertness, performance and vigilance were seen during (simulated) night shifts [65, 66]. Erman et al. [67] studied the effects on patient functioning and quality of life in a SWSD population using modafinil. Results imply that modafinil not only has an effect on alertness and wakefulness but also improves the patients' well-being. Modafinil did not affect the ability to sleep during daytime and was well tolerated both in the 200 mg and the 300 mg dosage [67]. Czeisler et al. [68] investigated the efficacy and safety of 200 mg modafinil in a population of shift workers suffering from SWSD. A modest improvement in alertness and performance was seen with modafinil. In addition, fewer patients using modafinil, as compared with placebo, reported car accidents or near-miss accidents on their way home after work (29 percent *versus* 54 percent). The question remains if this refinement is sufficient for patients to drive more safely. In addition, modafinil only improves symptoms

of sleepiness, but does not affect the cause of SWSD. Furthermore, a comparison between the use of modafinil and caffeine after extended wakefulness showed no superiority for modafinil, suggesting that caffeine would be a much cheaper substitute [69].

Hypnotic agents

Hypnotics may aid in promoting sleep, especially during the daytime when circadian processes may hinder sleep. A number of studies demonstrated a positive effect of triazolam [70], zopiclone [71, 72], zolpidem [73] and temazepam [74] on sleep in (simulated) shift work.

One study examined the residual effects of morning intake of midazolam (15 mg), triazolam (0.5 mg), temazepam (20 mg), and placebo on actual driving performance in the afternoon in a group of shift workers [75]. The effects were studied on the first and fifth day of treatment. Midazolam improved daytime sleep on several parameters. Triazolam had fewer but still beneficial effects, whereas temazepam had no positive effect on any of the sleep parameters. Results from the on-the-road driving test showed that temazepam did not impair driving. Midazolam had minor effects: a small increase in the standard deviation of the lateral position of the car (SDLP, an index for weaving of the car) was found on the fifth day of treatment. Triazolam seriously affected SDLP, steering behaviour, time out of lane and time to lane crossing. The effects were larger on day 1 than on day 5. These results suggest that triazolam, due to its residual effects, should not be recommended to shift workers. Temazepam is safe, but not very effective. Midazolam seems to be both safe and effective, at least for short-term use.

It has to be noted that intake of hypnotics should not be regarded as a permanent solution for shift work-related sleeping problems due to the risk of tolerance, dependence, and abuse.

Manipulating the circadian rhythm

Another approach in SWSD therapy is to manipulate the inner circadian rhythm. The main cause of SWSD is the inability of shift workers to adapt their habitual sleep-wake cycle to unusual working hours not coinciding with the normal sleep-wake pattern. By shifting the sleep phase, a beneficial alignment can be created.

The secretion of melatonin is controlled by the SCN, the body master clock, and is synchronized with the 24 hour light/dark cycle, showing high nocturnal plasma levels and low plasma levels during the day [76, 77]. Thus, melatonin can be seen as an important marker of the circadian phase [78] and a vital compound in sleep regulation. Exogenous melatonin, when taken at an appropriate time, can act as a chronobiotic. This means exogenous melatonin or comparable compounds are substances capable of manipulating the biological clock, i.e. advancing or delaying the phase depending on the time of administration. The minimum core body tem-

perature (T_{min}), close to the middle of the last part of sleep, can be seen as a turning point. Exogenous administration subsequent to the T_{min} results in a phase delay. When taken in the late evening (before T_{min}), this results in a phase advance. In this way it is possible to shift the biological clock by advancing the sleep period so that it concurs with daytime, thus correcting the misalignment of working hours and the normal sleep-wake pattern [78]. However, the efficacy of exogenous melatonin is a matter of discussion, reflected in the different results found in various studies in shift workers. Two studies suggest that melatonin (5 mg, and 1.8 mg extended release, respectively) aids in improving sleep in shift work [79, 80], one study demonstrated moderate effects of melatonin (10 mg) [81], and three other studies with dosages ranging from 1 to 6 mg [82–84] did not find any effect of melatonin compared to placebo [85]. The influence of melatonin on driving performance was assessed in one study using a driving performance test battery comprising a number of driving-related computer tasks [86]. Melatonin had no significant effect on several tests, except for selective attention. However, the values remained within the normal range.

Phase shifting can also be induced by influencing a subject's exposure to (bright) light. Light exposure prior to T_{min} delays the sleep phase and a phase advance is achieved by late night light exposure. Light intensity and duration influence the extent of shifting. The use of bright light can be applied during night shifts or phase shift schedules can be designed to realize the sleep phase shift gradually. In addition to the exposure to bright light during nightly shifts, unwanted light exposure during the day must be avoided. When driving home from a night shift, daylight can counteract the phase-advancing effects accomplished by nocturnal exposure to bright light. The use of goggles during the drive home, immediately (or at least as soon as possible) going to bed and creating a dark sleep environment should prevent this. Nonetheless, it is hard to comply with these circumstances and difficulties rearranging the sleep-wake pattern into a regular pattern should be taken into account. Regarding the use of melatonin as a chronobiotic the unwanted light exposure should be taken into consideration, since the phase-advancing effects of melatonin administration during the day can be neutralized by daylight exposure [78]. The effects of melatonin or exposure to bright light on actual driving performance have not been examined yet.

Discussion and conclusions

Shift work can lead to disrupted sleep-wake regulation, which in turn can result in insomnia and excessive sleepiness. The two main effects, drowsy driving and falling asleep behind the wheel, pose a great threat to traffic safety.

Epidemiological data presented in this chapter show that shift workers experience higher levels of drowsiness when driving after shift work and significantly more traffic accidents are reported compared to drivers with a regular daytime job. Surprisingly few studies examined driving performance: four driving simulator

studies examined shift workers and none of them included patients with SWSD. Only one study examined actual driving performance in an on-the-road driving test. This study assessed the effects of several hypnotics, but not the effects of shift work *per se*.

Various factors make research in shift work difficult and require proper screening of the specific uniform sample of shift workers that one wants to study. These factors include shift type, shift duration, number of consecutive days on a shift type, speed of rotation, direction of rotation, health, social conditions, job type, and individual traits.

The negative effects of shift work remain unrecognized or are at least underestimated. Managers should take sleep-related complaints seriously and aid their employees in recognising sleep-related problems and their remedies. As shift work often occurs in highly competitive economical environments, this may encompass a large part of the problem.

A number of easily implementable countermeasures, such as wearing goggles after the night shift, light therapy and sleep hygiene measures help to adapt to irregular working hours, but compliance can be low. Modafinil is regarded as a promising candidate in the treatment of SWSD, but specific trials on the effects of modafinil on traffic safety in sleep-deprived shift workers have not been conducted yet. Though the use of modafinil could reduce excessive sleepiness and therefore improve patients' health and well-being, it is still unclear whether modafinil is able to have a positive effect on driving performance.

In conclusion, shift work is a vital part of our society, but its consequences on driving ability have to be taken seriously. Future studies should identify the mechanisms leading to driving impairment in shift workers in order to create optimal countermeasures.

Future studies should:

- establish the effects of different types of shift work on actual driving: on-the road studies during normal traffic should be performed
- elucidate the influence of personal characteristics on the ability to adapt to shift work
- examine the effects of different treatment options on driving performance
- examine the risks of flexible working schedules

Box 4

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Effects of anxiolytics on driving

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Abstract

Most of the currently used anxiolytic agents act *via* GABA or serotonin. The latter include drugs traditionally classified as antidepressants, which are reviewed in the next chapter. This chapter reviews the results of ten experimental studies investigating the effects of anxiolytics on driving performance using over-the-road tests. Results show that only the serotonergic drugs (buspirone, ondansetron and ritanserin) had a low potential for impairment. All GABA-agonists (diazepam, lorazepam, oxazepam, clorazepate, alprazolam, alpidem, suriclone) had moderate to severely impairing effects on driving in the doses studied. Impairment was clearly dose dependent, and increased on average with increasing blood concentrations. However, most studies analyzing correlations between drug concentrations in plasma and effects on driving performance found low and non-significant correlations, indicating that prediction of impairment from blood concentrations is problematic.

Furthermore, tolerance was found to develop only very slowly, and impairing effects did not seem to be counteracted by improvement in anxiety symptoms. Finally, subjects seemed relatively unaware of the effects of the drugs. Awareness of these effects was only seen with severe objective impairment, indicating that patients should be warned explicitly about the risks associated with using these drugs by their physicians or pharmacists.

Introduction

Anxiety symptoms are common in the general population. Symptoms may be mild, transient and without associated impairment in social and occupational functioning, but many patients are troubled by severe and persistent symptoms that may cause significant personal distress, impair function and reduce quality of life. Epidemiological studies indicate that anxiety disorders have a 12-month prevalence of approximately 15% and a life-time prevalence of approximately 21%, with an

overall male:female ratio of 1:2 across the age range. Individual disorders are less frequent, with estimated 12-month prevalence rates of 7.6% for specific phobias, 2.3% for panic disorder, 2.0% for social phobia, 1.5% for generalized anxiety disorder, 1.2% for posttraumatic stress disorder, and 0.7% for obsessive compulsive disorder [1]. Coexisting depressive symptoms are common.

In spite of the wide spectrum of disorders the pharmacotherapeutic interventions are quite similar. Most of the currently used anxiolytic agents act *via* GABA or monoaminergic neurotransmitters, mainly serotonin [2]. For much of the second half of the twentieth century the benzodiazepines, such as chlordiazepoxide (Librium), diazepam (Valium), oxazepam (Serax), clorazepate (Tranxene), lorazepam (Ativan) and alprazolam (Xanax), were the mainstay of the treatment of anxiety. Despite concerns about their long-term safety, they remain an important therapeutic option. Their anxiolytic effects have an immediate onset and, in contrast to many other drugs, they do not cause a worsening of anxiety when therapy is initiated. Benzodiazepines are generally well-tolerated, although side-effects such as sedation, impaired psychomotor performance and loss of balance may be problematic. Several epidemiological studies report associations with road traffic accidents, and with falls and fractures in the elderly.

Most other currently registered anxiolytic drugs act by modifying monoaminergic transmission, chiefly serotonin (5HT). Drugs traditionally classified as antidepressants were shown to have anxiolytic effects and some are now primarily used for the treatment of anxiety. Serotonergic drugs, such as antidepressants and buspirone, do not exceed benzodiazepines in terms of efficacy, but better tolerability and generally low potential for sedation have led to their adoption as first-line treatments for anxiety disorders. In particular the SSRIs as a class are now widely considered to be appropriate first-line anxiolytic drugs [1]. A major drawback in clinical practice is their slow onset of therapeutic effects, and the potential of acute doses to be anxiogenic. For these reasons, benzodiazepines are being used to cover this initiation period.

Scope of this review

This review will focus on the effects of benzodiazepine anxiolytics. For reviews of the effects of antidepressant drugs, including SSRIs and other drug classes used to treat anxiety, the reader is referred to respective chapters in this book. The review begins with a short summary of epidemiological evidence showing that risks for traffic accidents are increased with the use of benzodiazepine anxiolytics. Next, available data from experimental studies using over-the-road driving tests will be reviewed and compared to the effects of alcohol. In light of recent developments towards the establishment of thresholds for drug concentrations in blood while driving, available data on the relationship between driving impairment and drug concentrations will also be reviewed.

Epidemiological studies

Although one can imagine many practical consequences of benzodiazepine sedation, only a few have been strongly confirmed in well controlled epidemiological studies. The use of benzodiazepines has been shown to substantially increase patients' risk of becoming involved in car accidents, and also to increase the risk of falling and hip fractures in elderly patients [3]. Benzodiazepines are the most frequently detected licit drugs other than alcohol in drivers, and several studies show that users of benzodiazepine anxiolytics are over-represented in traffic accidents [4–10].

Estimated risks vary from approximately 1.5 to 13.5, depending on factors related to the drug (e.g. dose, half-life, and duration of treatment), the subject sample (e.g. age and gender), and the study design (e.g. case crossover *vs*. case control). In general, risks for traffic accidents in users of anxiolytics may be increased by approximately 50%. For example, Ray et al. found an odds ratio (OR) of 1.5 (95% CI 1.1–2.0) in elderly users of benzodiazepine anxiolytics (diazepam, lorazepam, chlordiazepoxide, clorazepate) [4]. Hemmelgarn et al. report similar risks in elderly users of long half-life benzodiazepines (OR 1.45, 95% CI 1.1–1.9 for clonazepam, diazepam, clorazepate, chlordiazepoxide, flurazepam and nitrazepam). In their study, risks were not increased in users of benzodiazepines with shorter (<24 h) half-lives [4]. In line with this, a case-crossover study by Barbone et al. found an OR for benzodiazepine use of 1.62 (95% CI 1.24–2.12), which was mainly attributable to benzodiazepine long half-life anxiolytics (OR 2.2, 95% CI 1.5–3.1) [8].

A large prospective cohort study by Neutel and colleagues examined traffic accident risks over a two month period after filling a prescription for a benzodiazepine anxiolytic (diazepam, lorazepam and oxazepam) in drivers of 20 years and older [5, 7]. They found that risks for accidental injury within the first four weeks after prescription was 2.5 times greater than that of controls. Analysis of risks by week after prescription suggests this was mainly due to very high risks in the first week, as OR was 13.5 in the first week and decreased to statistically nonsignificant ORs of 1.9, 1.4 and 0.8 in the three weeks thereafter [5]. Other studies confirm that risks are highest in the first week after prescription and diminish thereafter, possibly reflecting development of tolerance or a reduction in use after the first week [6, 10].

Neutel and colleagues also found males to have risks that were 3.6 times that of females, and users aged over 60 years to have lower increased risk after use of a benzodiazepine than their younger counterparts (OR 2.8 and 3.2, respectively [5, 7]). Findings by Barbone et al. confirm that risks increase more in young (<45 years) than older drivers, but the difference between men and women in their study was not significant [8]. A possible explanation is that females and the elderly are more likely to adjust their driving behaviour (e.g. reduce exposure) when prescribed medication that can impair their performance.

In summary, use of benzodiazepine anxiolytics is clearly associated with increased risks for traffic accidents. Risks are highest in the beginning of treatment and seem most pronounced in younger male drivers.

Table 1 Summary of designs and results of studies assessing the effects of anxiolytics on driving using a standardized highway driving test. Effects on driving as measured by Standard Deviation Lateral Position are classified as not significant (*ns*), or as equivalent to blood alcohol concentrations (BAC) at legal limits of 0.5, 0.8 and 1.0 mg/ml.

Study nr	Subjects	Design	Reference condition	Anxiolytic treatments	Effects on SDLP equivalent to alcohol with BAC (mg/ml)		References
					acute	*subchronic*	
1	9 police driving instructors (m) aged 24–34 yrs	Single dose, Cross-over	placebo	diazepam 5 mg	ns	–	11
				diazepam 10 mg	>1.0	–	
2	15 healthy volunteers (m) aged 25–34 yrs	Single day, Cross-over	placebo	buspirone 5 mg t.i.d.	<0.5	–	12,13
				buspirone 10 mg t.i.d.	<0.5	–	
				diazepam 5 mg t.i.d.	0.5–0.8	–	
				lorazepam 1 mg t.i.d.	>1.0	–	
3	8 healthy volunteers (m) 8 patients (m) aged 25–40 yrs	Single day, Cross-over	placebo	clorazepate 5 mg t.i.d.	0.5	–	14,15
				oxazepam 30 mg t.i.d.	0.5–0.8	–	
				lorazepam 0.5 mg t.i.d.	0.8–1.0	–	
4	18 healthy volunteers (m) aged 25–36 yrs	7 days, crossover	placebo	ritanserin 5 mg b.i.d.	–	ns	16,17
				lorazepam 1.5 mg b.i.d.	–	>1.0	
5	24 patients (m/f) in 2 groups aged 18–50 yrs	7 days run-in, 28 days treatment, 7 days washout	baseline	buspirone 15–20 mg/day	–	ns	18
				diazepam 15 mg/day	–	0.5–>1.0	

Table 1 *(continued)* Summary of designs and results of studies assessing the effects of anxiolytics on driving using a standardized highway driving test. Effects on driving as measured by Standard Deviation Lateral Position are classified as not significant (*ns*), or as equivalent to blood alcohol concentrations (BAC) at legal limits of 0.5, 0.8 and 1.0 mg/ml.

Study nr	Subjects	Design	Reference condition	Anxiolytic treatments	Effects on SDLP equivalent to alcohol with BAC (mg/ml)		References
					acute	*subchronic*	
6	16 healthy volunteers (m/f) aged 25–43 yrs	8 days, crossover	placebo	ondansetron 1 mg b.i.d. ondansetron 4 mg b.i.d. diazepam 5 mg t.i.d.	ns ns 0.5	ns ns >1.0	19, 22
7	18 healthy volunteers (m/f) aged 22–34 yrs	9 days, crossover	placebo	suriclone 0.2 mg t.i.d. lorazepam 0.5 mg t.i.d.	>1.0 >1.0	0.8 >1.0	20, 22
8	54 patients (m/f) in 3 groups aged 24–64 yrs	7 days run-in, 8 days treatment, 6 days washout	Baseline, placebo group	alpidem 50 mg b.i.d. lorazepam 2 mg b.i.d.	0.5–0.8 >1.0	0.5–0.8 >1.0	21, 22
9	20 healthy volunteers (m/f) aged 21–45 yrs	Single dose, crossover	placebo	alprazolam 1 mg IR	>1.0	–	23
10	18 healthy volunteers (m/f), aged 21–45 yrs	Single dose, crossover	placebo	alprazolam 1 mg IR alprazolam 1 mg XR	>1.0 0.5–0.8	– –	24

Experimental studies

Ten studies investigated the effects of anxiolytics on driving performance, using over-the-road tests on public roads in normal traffic, providing objective measures of driving performance (Table 1) [11–24].

The primary and most frequently used test is the *highway driving test* [11, 22, 25, 26]. This test evolved from studies on driver fatigue conducted in the US during the early 1970s, and was standardized for use in drug studies in the early 1980s. It has subsequently been used in at least 75 drug studies. The test involves subjects driving a specially instrumented car over a 100 km (61 miles) primary highway circuit while maintaining a constant speed and a steady lateral position between the boundaries of the slower traffic lane. Subjects are accompanied by a licensed driving instructor, who has access to dual controls. Speed and lateral position relative to lane delineation are continuously recorded during the one-hour drive by apparatus aboard the vehicle. After completion of the test the data are reduced to yield several measures, including the primary performance parameter, *Standard Deviation of Lateral Position* (SDLP, in cm). SDLP can be interpreted as an index of weaving or road tracking error. It is a reliable characteristic of individual driving performance (test retest r = 0.7 to 0.9) and has proven sensitive to many sedating drugs, such as anxiolytics, hypnotics, antidepressants and antihistamines (for reviews see others chapters in this book, and [3, 22, 26–30]).

Importantly, this test was calibrated for the effects of different doses of alcohol, which facilitates interpretation of the severity of effects of medicinal drugs on performance found in this test. In the alcohol calibration study 24 social drinkers were tested sober and after controlled drinking that raised blood alcohol concentrations (BACs) to 0.3, 0.6, 0.9 and 1.2 mg/ml [26, 31]. Since BACs were above the legal limit, driving took place on a 24 km closed highway circuit. Results showed that SDLP increased as an exponential function of BAC, which is in line with the relation between BAC and accident risk as estimated in the benchmark study by Borkenstein [32]. The mean relationship between SDLP and BAC was nearly perfect (r = 0.99), and BACs of 0.5, 0.8 and 1.0 mg/ml were associated with estimated mean changes in SDLP of 2.4, 4.1 and 5.3 cm. Based on these data, drug effects associated with mean increases in SDLP of 2.4 cm or more are considered clinically relevant, as they are equivalent to or higher than the effects of alcohol, while BAC is 0.5 mg/ml, which is the legal limit for driving a car in most countries. Significant drug effects on SDLP less than 2.4 cm are considered as minor (< BAC 0.5 mg/ml), effects between 2.4–4.1 cm are considered as moderate (BAC 0.5–0.8 mg/ml), and effects of 4.1 cm and more as severe (BAC > 0.8 mg/ml).

A secondary test used to objectively assess the effects of drugs on over-the road driving performance is the *car-following* test [33, 34]. In this test subjects drive an instrumented car over a secondary highway in normal traffic, and are instructed to follow a preceding (leading) instrumented car controlled by an experimenter at a fixed distance (between 15–30 m). While the two vehicles travel in tandem at a speed of 60 or 70 km/h, the experimenter in the leading car executes a number of sinusoidal deceleration-acceleration maneuvers using a modified cruise-control sys-

tem. Subjects are instructed to adapt their speed accordingly, in order to maintain a constant distance behind the leading car. Distance between cars, and speed of each car are recorded during driving and processed off-line to yield measures of phase delay or time lags, and headway variability, reflecting subjects' speed of responding and ability to keep a constant distance to the preceding car, respectively.

Benzodiazepine receptor agonists

Diazepam

Diazepam is a 1,4-benzodiazepine usually prescribed in daily doses between 5–40 mg. It is rapidly absorbed, and has a long half-life of 43 ± 13 hours, ranging between 40–100 hours if the contribution from active metabolites, nordiazepam, temazepam and oxazepam, is included. Its major metabolite is nordiazepam, which has a half-life of 40–99 hours. Therapeutic blood concentrations typically range between 100 and 1000 ng/ml. After single oral doses of diazepam 10 mg mean peak blood concentrations of 200–600 ng/ml (mean 410 ng/ml) were reached within 0.5–2.5 hours. Chronic daily dosing of 30 mg produced steady state concentrations between 700–1500 ng/ml (mean 1000 ng/ml) and nordiazepam concentrations of 350–530 ng/ml [35].

Diazepam's effects on highway driving performance in doses between 5 and 15 mg per day was measured in three studies. Results are shown in Figure 1.

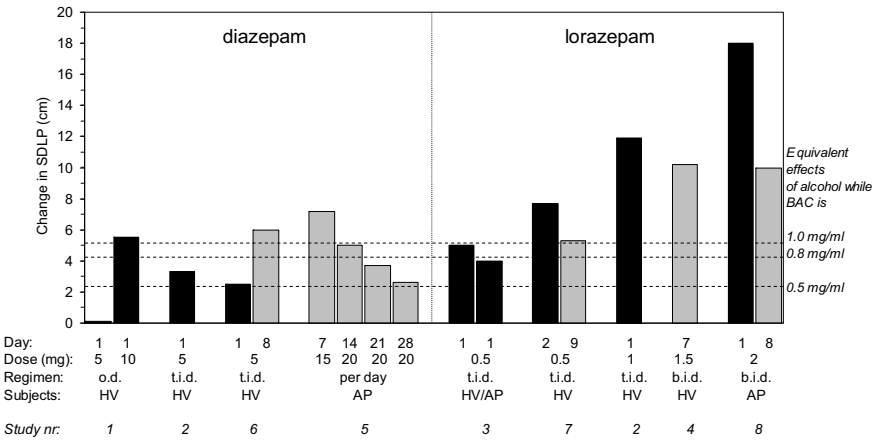

Figure 1 Acute (black bars) and subchronic (grey bars) effects of diazepam and lorazepam in various doses on Standard Deviation Lateral Position (SDLP) in the highway driving test in eight separate studies [11–22] with healthy volunteers (HV) and/or anxious patients (AP). Dotted lines indicate mean changes in SDLP observed with blood alcohol concentrations (BAC) of 0.5, 0.8 and 1.0 mg/ml in a previous study [31].

O'Hanlon and co-workers [11] assessed the acute effects of diazepam 5 and 10 mg in a double-blind, placebo-controlled, crossover study with nine healthy young male police driving instructors. Subjects performed the highway driving test in the evenings, one hour after drug or placebo administration. Diazepam 10 mg significantly increased SDLP as compared to placebo (Fig. 1, study 1), whereas diazepam 5 mg had no significant effects. Subjects seemed aware of the sedating effects of higher dose as performance changes were accompanied by a corresponding drop in subjective arousal measured using a visual analogue scale ($r = -0.79$).

In a subsequent study, Volkerts, Brookhuis and O'Hanlon [12, 13] examined the effects of a single-day treatment of diazepam 5 mg t.i.d. in a double-blind, placebo-controlled, crossover study with 15 male volunteers. Drugs and placebo were ingested at four hour intervals with the final dose occurring one hour prior to the driving test. Diazepam had moderate effects on SDLP (Fig. 1, study 2). Correlations between changes in driving performance and plasma concentrations of diazepam (mean 247 ng/ml, range 91–365 ng/ml) and nordiazepam (mean 18 ng/ml, range 6–30 ng/ml) were low ($r = 0.24$ and $r = 0.35$, respectively). Subjects' self ratings of driving quality and activation did not discriminate between treatments.

Van Veggel and O'Hanlon [19, 22] studied the acute and subchronic effects of diazepam 5 mg t.i.d. in a double-blind, placebo-controlled, crossover study with 16 male and female healthy volunteers. Highway driving performance was significantly impaired after the first 5 mg dose (Fig. 1, study 6). The effects were more severe after thrice daily dosing for one week. Unfortunately, no blood concentrations were measured in this study. Similar to the previous study, subject's self ratings of driving quality and activation did not differ between treatments.

A study in anxious outpatients [18] showed that tolerance to the impairing effects of diazepam 5 mg t.i.d. develops slowly. In this study 24 anxious patients (mean age 40 years) were randomly assigned to four weeks of double-blind treatment with diazepam 5 mg t.i.d. or buspirone 5 mg t.i.d. Treatment was preceded by one week single blind placebo run-in and followed by one week placebo wash-out. Diazepam significantly impaired driving during the first three weeks of treatment. Mean increase in SDLP was approximately 7 cm after one week of treatment, and slowly declined to approximately 2.5 cm after four weeks (Fig. 1, study 5). Although the latter difference was no longer significant, it is about the same as that observed with alcohol when BAC was at the legal limit of 0.5 mg/ml in a previous study [31]. Weekly plasma concentrations of diazepam (ranging between 450 and 650 ng/ml), and nordiazepam (ranging between 250 and 600 ng/ml) were not significantly related to changes in SDLP.

Lorazepam

Lorazepam is a 3-hydroxy benzodiazepine, structurally similar to oxazepam and temazepam. Its usual daily dose for adults is 2 to 3 mg per day, with a maximum of 6 mg per day, in divided doses. Lorazepam is metabolized by glucuronidation and

its half-life ranges between 9–16 hours. It has no active metabolites. After a single, 2 mg oral dose peak plasma concentrations of 18 ng/ml on average were reached at 2 hours and declined to 9 ng/ml by 12 hours [36].

Acute and subchronic effects of lorazepam in doses of 1.5 and 3 mg per day on highway driving performance have been evaluated in four double blind, placebo controlled, crossover studies [12, 14, 17, 22]. A fifth study compared acute and subchronic effects of lorazepam 2 mg b. i. d. to placebo in two groups of anxious patients [21, 22]. Results are shown in Figure 1.

Two studies examined effects of lorazepam 1.5 mg per day. In the first study [14], single-day treatment with lorazepam 0.5 mg t. i. d was found to severely impair highway driving in eight healthy young males and eight male anxiety patients, aged between 25 and 40 years. Increases in SDLP were moderate to severe and comparable in both groups (Fig. 1, study 3). In addition, subjects drove at a more variable speed. Healthy subjects seemed aware of the impairing effects of lorazepam as they rated their quality of driving as significantly worse than placebo, but patients' ratings did not differ significantly between treatments. Mean serum concentrations of lorazepam in blood samples collected after the driving test were similar in patients and healthy subjects, i.e. 10.6 ng/ml.

Uiterwijk and O'Hanlon [22] treated 18 healthy subjects (nine females; mean age 25 years) for nine days with lorazepam 0.5 mg t.i.d. and measured effects on highway driving and car following performance two hours following the afternoon doses on day 2 and day 9, respectively. Consistent with previous findings, lorazepam severely impaired driving on day 2 and 9 (Fig. 1, study 7). On day 2 lorazepam also impaired subjects' ability to drive at a constant speed, and in the car following test it slowed reaction times to speed changes in the preceding car and impaired subjects' ability to maintain a constant distance between cars. These effects were no longer significant on day 9. Although there was a trend, subjects did not indicate feeling significantly less active after the use of lorazepam. No blood samples were collected.

Two other studies examined the effects of lorazepam 3 mg per day in male volunteers [12, 17]. Volkerts, Brookhuis & O'Hanlon [12] examined the acute effects of lorazepam 1 mg t.i.d. after a single day treatment in a study with 15 healthy young males. Effects were measured in the evening one hour after the last dose. Results showed that lorazepam at this dose severely impaired driving performance. The mean increase in SDLP was 11.9 cm (Fig. 1, study 2), which is worse than effects seen with alcohol when BAC was 1.5 mg/ml [31]. In addition, subjects drove significantly faster and with a more variable speed following lorazepam. They were aware of the impairing effects as they rated the quality of driving with lorazepam as significantly worse than with placebo, yet subjects did not feel significantly less active. Mean serum concentrations of lorazepam in blood samples collected 15 min before driving were 65 (range 23–131) ng/ml. A significant linear correlation ($r = 0.45$, $p < 0.03$) was found between changes in SDLP from placebo and serum concentrations.

Van Laar, Volkerts and Verbaten [17] found that the effects of lorazepam 3 mg per day remain severe for at least one week. After seven days of treatment in 18 healthy males, lorazepam 1.5 mg b. i. d. increased SDLP by approximately 10 cm compared to placebo (Fig. 1, study 4). Results from multiple sleep latency tests performed before and after driving supported the fact that that subjects were significantly more sedated and sleepy when using lorazepam than placebo, as shown by shortened sleep onset times. Although subjects did notice that their driving quality was worse following lorazepam compared to placebo, they did not indicate feeling less active. Mean plasma concentrations of lorazepam in blood samples collected after driving were 27 (range 5–46) ng/ml. There was no correlation ($r = 0.08$) between changes in SDLP from placebo and plasma concentrations.

Finally, effects of lorazepam 4 mg per day were studied in anxious patients by Vermeeren, Swijgman and O'Hanlon [21, 22]. In this study two groups of anxious patients participated in a parallel group design with 21 days of treatment. Patients were randomly assigned to eight day double-blind treatment with lorazepam 2 mg b. i. d. or placebo, preceded and followed by single, blind placebo treatment. Driving tests were performed at the start of the placebo run-in (baseline), and at the start and end of the double blind placebo or lorazepam treatment period (day 1 and 8). Results showed that baseline driving performance was normal and did not differ between groups. Lorazepam's effects on driving were severe on both days, although there was some reduction in severity of effects after one week (Fig. 1, study 8). Speed variability was also significantly increased on both days in the lorazepam group. In contrast, the lorazepam group only judged the quality of their driving different from baseline and placebo on the first day of treatment, and subjective ratings of sleepiness and activation did not differ between groups on any day. Average scores on the Hamilton anxiety rating scale decreased similarly in both groups from placebo run-in to the last day of treatment, i.e. from 23.4 to 17.7 in the lorazepam group, and from 24.8 to 16.9 in the placebo group. No blood samples were collected in this study.

Oxazepam

Oxazepam is an active metabolite of diazepam, and is usually prescribed in daily doses between 30–120 mg. After a single oral dose of 15 mg, peak concentrations of 310 ng/ml were observed at 1.5 hours, and after a single dose of 45 mg peak concentrations of 1060 ng/ml were observed at 2 hours. Oxazepam has an intermediate half-life of 8 ± 2.4 hours [37].

In the study by Brookhuis and Borgman (study 3) acute effects of oxazepam 10 mg t.i.d. were moderate and similar in male anxiety patients and healthy volunteers (Fig. 2) [14]. Mean serum concentrations of oxazepam in blood samples collected after the driving test were similar in patients and healthy subjects, i.e. 305 ng/ml. Neither group indicated that their driving quality with oxazepam had been significantly different from placebo.

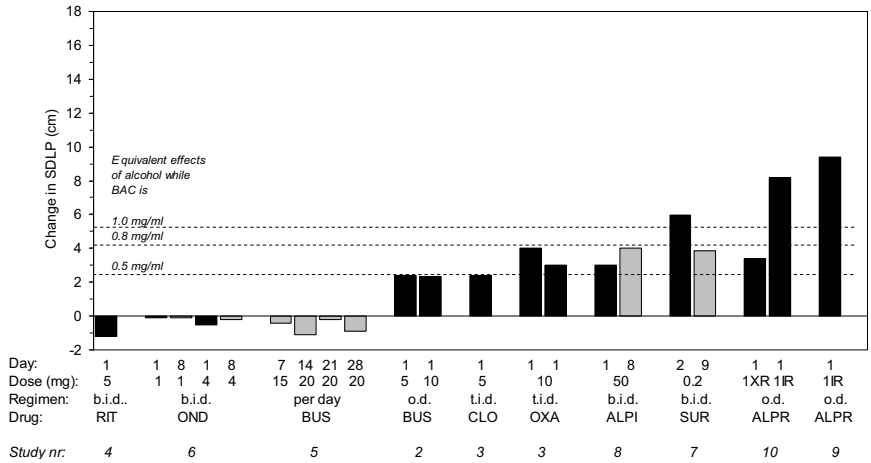

Figure 2 Acute (black bars) and subchronic (grey bars) effects of ritanserin (RIT), ondansetron (OND), buspirone (BUS), clorazepate (CLO), oxazepam (OXA), alpidem (ALPI), suriclone (SUR) and alprazolam (ALPR) in various doses on Standard Deviation Lateral Position (SDLP) in the highway driving test in eight separate studies [12–24]. Dotted lines indicate mean changes in SDLP observed with blood alcohol concentrations (BAC) of 0.5, 0.8 and 1.0 mg/ml in a previous study [31].

Volkerts and colleagues [38] examined the residual effects of oxazepam 50 mg administered as a hypnotic at bedtime on driving performance the next day in healthy male volunteers. Results showed significant residual impairment of driving in the morning, between 10 and 11 hours after administration. Effects were no longer significant in a repetition of the driving test in the afternoon, between 16–17 hours after administration.

Clorazepate

Clorazepate (dipotassium chlorazepate) is a long-acting benzodiazepine usually prescribed in daily doses between 15–60 mg per day. The drug is rapidly absorbed and metabolized by decarboxylation to form nordiazepam. Clorazepate itself has a very short half-life (approximately 1 h). After single oral administration of 15 mg, mean peak concentrations of 20 ng/ml clorazepate are reached within 30 minutes, and mean peak concentrations of 160 ng/ml nordiazepam are reached approximately after 2 hours. Chronic use of 22.5 and 50 mg/day produced average nordiazepam concentrations in plasma of 640 ng/ml and 1590 ng/ml, respectively [37]. In the study by Brookhuis and Borgman (study 3) clorazepate 5 mg t. i. d had minor to moderate impairing effects in male anxiety patients and healthy volunteers (Fig. 2) [14]. Mean serum concentrations of nordiazepam blood samples collected after the driving test were 156 ng/ml.

Alprazolam

Alprazolam is a 1-4,triazolobenzodiazepine derivative that has been available as a prescription drug for the relief of anxiety since 1980. Its elimination half-life ranges between 10 and 18 hours (mean 13 hours). It is available in an immediate release (IR) and an extended release (XR, Retard) formulation. The recommended starting dose of alprazolam IR is 0.25 or 0.5 mg t.i.d., which may be followed by divided dose escalation to a maximum of 4 mg/day. After a single oral administration of alprazolam 1 mg IR peak plasma concentrations ranging between 12 and 22 ng/ml are reached within 0.7 to 1.8 hours. Steady state plasma levels in patients chronically using 3, 6 and 9 mg daily averaged 29 ng/ml, 61 ng/ml, and 102 ng/ml, respectively. Alprazolam XR produces peak plasma concentrations that are about 50% of a similar dose of the immediate release formulation and occur between 5 and 12 hours after administration [37, 39].

The acute effects of alprazolam 1 mg on over-the-road driving have been studied in two studies [23, 24]. Verster, Volkerts and Verbaten [23] administered single doses of alprazolam 1 mg (immediate release formulation) and placebo in the morning to healthy volunteers and measured effects driving one hour later, and on laboratory tests of tracking, divided attention and memory scanning 2.5 hours later (study 9). Results showed that alprazolam 1 mg severely impaired performance in all tests. The mean increase in SDLP was comparable to effects of alcohol while BAC is 1.5 mg/ml (Fig. 2) [31]. The drug also impaired subjects' ability to maintain a constant speed. Subjects were clearly aware of the impairing effects as shown by significant decreases in subjects' ratings of their driving quality and alertness. No blood samples were collected in this study.

Leufkens and collaegues [24] compared the effects of immediate and extended release formulations of alprazolam 1 mg to that of placebo in healthy young volunteers (study 10). Effects on driving were assessed at the time of peak concentrations after extended release, between 4 and 5 hours after intake, and additional effects on laboratory tests of divided attention and inhibitory control were assessed at 1, 2.5 and 5.5 hours after ingestion. Similar to the previous findings, the immediate release formulation of alprazolam had severe effects on driving (Fig. 2). Effects of the extended release formulation were considerably less, but still moderately severe. Effects on driving were supported by significant impairing effects of both alprazolam formulations on performance in both laboratory tasks between 1 and 6 hours after ingestion. Mean serum concentrations of alprazolam in blood samples collected before and after testing (i.e. approximately at 1 and 6 hours after ingestion) were 5 and 11 ng/ml for the IR formulation and 2 and 9 ng/ml for the XR formulation, respectively. These levels are comparable to or lower than average steady state levels reported for patients chronically using alprazolam 3 mg per day [40]. This suggests patients chronically using alprazolam regularly are significantly impaired, unless they develop pharmacodynamic or behavioral tolerance to the sedative effects. In their review of the clinical efficacy and behavioral toxicity of alprazolam Verster and Volkerts [41] report that after 1 to 3 weeks of daily administration, alprazolam no longer produced significant impairment in most tests, whereas the effects of

acute doses were significant in the majority of tests. Although the authors argue this may partially be explained by learning effects resulting from repeated testing may, receptor downregulation has also been shown to occur with repeated use of alprazolam [42]. Verster and Volkerts [41] stress, however, that pharmacodynamic tolerance lasts only as long as drug therapy is continued on a daily basis, which is frequently not the case due to as-needed use or poor compliance.

Alpidem

Alpidem is an imidazopyridine anxiolytic, related to zolpidem. Alpidem primarily acts as a partial agonist at benzodiazepine receptors containing alfa-1 subunits, but also shows affinity for alfa-3 subunits. The recommended dose varies between 75–150 mg per day. Alpidem was withdrawn from the market in most of the world following reports of severe liver damage. Alpidem 50 mg b.i.d. (Fig. 2, study 8) had moderately severe effects on the driving of anxious patients during the first week of treatment [21, 22]. There were no significant effects on subjective ratings of driving quality and alertness. No blood samples were collected in this study.

Suriclone

Suriclone is a cyclopyrrolone benzodiazepine receptor agonist anxiolytic, structurally related to the hypnotic zopiclone. Uiterwijk and O'Hanlon (Fig. 2, study 7) showed that suriclone 0.2 mg t.i.d. had significant effects on the driving of healthy male and female volunteers on day 2 and 9 of treatment [22]. Effects on the first day were severe. After a week they were reduced, but still moderate. On the first day suriclone also impaired performance in the car-following test. In line with this, subjects indicated feeling significantly less active with suriclone. No blood samples were collected in this study.

Serotonergic anxiolytics

Buspirone

Buspirone is the first drug from the chemical family of azapirones that was introduced in Europe in 1985 and in the United States at the end of 1986 [43]. It is structurally related to gepirone, which is currently under FDA review for treatment of anxiety. Buspirone acts as a partial agonist at postsynaptic serotonin 5HT1A receptors in the limbic system and full agonist at autoreceptors in the Raphe nuclei. Acute dosage inhibits 5HT release but this recovers with continued administration, presumably due to downregulation of the 5HT1A autoreceptors and postsynaptic 5HT2 receptors. In addition, buspirone has a moderate affinity for presynaptic dopamine D2 receptors. Its anxiolytic effects take several weeks to emerge. Buspirone

is usually prescribed in doses between 15 and 30 mg per day. Following oral administration, plasma concentrations of unchanged buspirone are very low and variable between subjects, because it undergoes extensive first-pass metabolism. On average, only 4 % of an oral dose enters the systemic circulation. It has a weakly active metabolite, 1-pyriminidylpiperazine (1-PP). After a single oral dose of buspirone 20 mg, peak plasma concentrations of between 1 and 6 ng/ml were observed within approximately one hour. It has an elimination half-life of 2–3 hours. Buspirone has a low potential for sedation [44].

Single-day treatments of buspirone 5 and 10 mg t.i.d. (Fig. 2, study 2) were found to have significant adverse effects on driving of 15 healthy males [12]. However, effects seemed self limiting as the results failed to show any increase in impairment when the dose was doubled. Buspirone had no significant effects on subjective ratings of driving quality and activation. Mean serum concentrations of buspirone and 1-PP were also found to be comparable following the low and high dose, i.e., 2.7 (range 1.4–5.3) ng/ml and 7.4 (1.6–14.9) ng/ml, respectively, after 5 mg t.i.d., and 2.9 (range 1.4–3.9) ng/ml and 6.3 (1.7–12.8) ng/ml respectively, after 10 mg t.i.d. No relationship was found between changes in SDLP and serum concentrations.

In contrast, buspirone in daily doses of 15 to 20 mg (Fig. 2, study 5) had no adverse effects on driving performance in 12 anxious outpatients during a four week treatment period, while diazepam 15 mg clearly impaired driving in a second group of 12 patients [18]. Mean SDLP measured at the end of weeks 1, 2, 3 and 4 of buspirone treatment was normal and similar to that at the end of a placebo run-in and placebo wash-out week. At the same time, patients' anxiety scores were significantly reduced during treatment and wash-out as compared to placebo run-in. Mean plasma concentrations of buspirone per week varied between 0.9 and 1.1 ng/ml, and of its metabolite, 1-PP, between 3 and 3.5 ng/ml. Correlations between change in SDLP and plasma concentrations were low and not significant.

Ritanserin

Ritanserin is a potent, long acting 5HT2a and 5HT2C receptor antagonist that was being developed as a potential treatment for anxiety, depression, headache, psychosis and substance dependence. Development has been discontinued, however. Van Laar and colleagues [17] showed that ritanserin 5 mg b. i. d. had no adverse effects on driving following seven days of treatment (Fig. 2, study 4).

Ondansetron

Ondansetron is a 5HT3 receptor antagonist that was under investigation for the treatment of anxiety, but is now registered as an antiemetic. Van Veggel and O'Hanlon [22] found that ondansetron 1 and 4 mg b. i. d had no significant effects on driving on the first and last days of an eight day treatment period in a double-blind placebo controlled crossover study with 16 healthy volunteers (Fig. 2, study 6). No blood concentrations were measured in this study.

Discussion and conclusions

All GABA-agonists had moderate to severely impairing effects on performance in the highway driving test in the doses used. Only the serotonergic drugs (buspirone, ondansetron and ritanserin) had a low potential for impairment.

In the first week of continuous treatment, effects were seen to decrease (e.g. lorazepam) [22]. Tolerance seems to develop only very slowly, shown by the significant impairing effects of diazepam over the first three weeks of treatment in patients [18]. Drug effects seemed comparable in healthy volunteers and patients, and both studies in patients also indicate that the drug-induced impairment of driving is not counteracted by improvement in anxiety symptoms [14, 18, 22].

Drug effects are clearly dose dependent and increase on average with increasing blood concentrations. However, predicting impairment in individual cases from blood concentration seems problematic. Most studies analyzing correlations between blood concentrations of the drugs and effects on driving performance found only low and non-significant correlations [12, 14, 17, 24], except one [12]. Only serum concentrations after a single-day treatment with lorazepam 1 mg t.i.d. were positively related to impairment, which may be due to the wide range of concentrations and impairing effects found after this dose. The mean increase in SDLP produced by this drug-dose was nearly 12 cm, which is one of the most impairing effects measured in healthy volunteers with any psychoactive drug tested in this model.

Finally, subjects seem relatively unaware of the effects of the drugs. Moderately impairing drug-doses were not associated with significant changes in subjective ratings of driving quality and activation. Awareness of these effects was only seen with severe objective impairment (i.e. ΔSDLP > 5 cm). This indicates that patients should be warned explicitly about the risks associated with using these drugs by their prescribing physician or pharmacist, as lack of awareness of moderately impairing effects can add to the risks.

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Antidepressants and traffic safety

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Abstract

Depression is a common disease that is often pharmaceutically treated with tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Both groups of drugs have proven to be effective in treating depressive symptoms, however they differ in adverse effect profile. This chapter discusses their effects on driving ability. On the road driving tests have shown that TCAs such as imipramine, doxepine and amitriptilyne significantly impair driving performance after single dose administration. However, after one to two weeks of daily treatment tolerance developed and no significant driving impairment was reported. Sedative antidepressants such as mianserin and mitrazapine administered at bedtime produce significant driving impairment the morning following single dose administration and after one week of daily treatment. In contrast, SSRIs such as fluoxetine and paroxetine had no significant effects on driving ability. Also, venlafaxine did not affect driving performance. The chapter concludes by discussing that untreated depression impairs driving ability and that reported somnolence correlates significantly with reduced driving performance.

Introduction

Depression is a common disease affecting up to 15% of the population at least once during their lives. The prevalence of depression is two to three times higher in women as compared to men. According to the World Health organization, by 2030 depression will be the second highest cause of medical disability, preceded by HIV and AIDS. Patients who suffer from depression are often treated with antidepressant drugs such as tri-cyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs). Unfortunately, a number of antidepresant drugs can have side effects that impair cognitive and psychomotor performance, including the ability to drive a car. These adverse effects can be explained by their mechanism of action.

For example, TCAs act at cholinergic, adrenergic and antihistamine receptors, which may result in cognitive impairment and sedation. In contrast, SSRIs and related antidepressants act at the serotonin receptor and have little affinity for cholinergic, adrenergic and antihistamine receptors.

Most of those who use antidepressants are outpatients and therefore it is likely that they drive a car. Over the past 25 years several studies have been performed to examine the effects of several antidepressant drugs on driving ability. This chapter will discuss the studies that have been performed using the on-the-road driving test during normal traffic. Most antidepressants were examined in double blind, placebo controlled studies and tested after acute administration (after one day) or after one or several weeks of daily treatment. Most studies were performed in healthy volunteers [1–10], except for two studies performed in depressed outpatients [11–12]. Oxaprotiline, levoprotiline and brofaromine had no significant effects on driving performance, but were not marketed [10–12] and will therefore not be discussed in this chapter. Studies with other antidepressants are summarized below.

TCAs

Various TCAs have been tested using the on-the-road test, including amitriptyline (25 mg tid) [1, 4], doxepine (25 mg tid) [1–3] and imipramine (50 mg bid) [5]. After the first dose on the first day of treatment, significant impairment was observed with Standard Deviation of Lateral Position (SDLP) increments relative to placebo that are comparable to those seen with Blood Alcohol Concentration (BAC) >0.08%. After one week of treatment, tolerance developed and no significant driving impairment was found. Given the adverse effects noted with TCAs, nocturnal dosing is a way to increase the time between drug use and driving. On the road driving tests performed 16 to 18 hours after intake of dothiepin (75 mg) showed no significant difference from placebo after one and eight days of treatment [8]. After this week, two weeks of nocturnal treatment with 150 mg dothiepin followed. Again, no significant impairment was found after two weeks of treatment.

Mianserin

Mianserin (a α2 antagonist) significantly impaired driving two hours after treatment on the first treatment day, comparable to a BAC of 0.10% [1, 6–7]. In the studies that examined mianserin, due to pronounced sedation 10–50% of subjects were unable to complete their driving test on the first day of treatment. After one week of treatment (10 mg tid) driving impairment was less pronounced but still significantly worse when compared to placebo, and driving persisted impaired even after two weeks of daily treatment with mianserin (ΔSDLP equivalent to a BAC >0.05%).

Nocturnal administration of mianserin (15 mg daily for seven days followed by eight days of 30 mg daily) significantly increased SDLP after one week of treatment

with 15 mg daily, but impairment was modest and below that observed with a BAC of 0.05 % [9]

Mirtazapine

Mirtazapine (30–45 mg/day) significantly impaired driving performance on the second test day [10]. On day nine and 16 of daily treatment with mirtazapine, no significant differences from placebo were found. Nocturnal administration of mirtazapine (30 mg daily for seven days followed by 60 mg daily for another eight days) produced impairment on the first (single dose) and last day of treatment [9]. When compared to alcohol, SDLP increments were less than observed with a BAC of 0.05 % on all test days.

Moclobemide

Moclobemide is a reversible inhibitor of monoamine oxidase A. Moclobemide (200 mg bid) was tested on day one and eight of treatment [6]. On both test days, no significant effects on driving performance were found.

SSRIs and related compounds

Fluoxetine (20 mg) did not impair driving performance on day one, eight and 22 of treatment [8]. Another SSRI, paroxetine (20 mg and 40 mg) did not impair driving on the first day of treatment and after one week [13]. Escitalopram (10–20 mg/day) did not affect driving performance on day two, nine and 16 of daily treatment [10].

Nefazodone, a serotonin receptor antagonist and reuptake inhibitor, improved driving on day one and eight of daily treatment with 100 mg. On day one, the 200 mg dose also significantly improved driving, whereas after one week the 200 mg dose significantly impaired driving [5]. The effects of nefazodone were significant but of little relevance. When compared to alcohol effects, they were below a BAC of 0.05 %. Venlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI), also did not affect driving performance after acute and subchronic administration (37.5 mg bid) [7].

Combined use of antidepressants and benzodiazepines

A study of depressed outpatients examined the effects of fluoxetine (20 mg qam) or moclobemide (150 mg bid) on driving ability. About 80 % of patients were also treated with benzodiazepines. Driving tests were performed in week one, three and

six of daily treatment. In the first week, no significant effects on driving performance were reported. Patients using benzodiazepines, in whom metabolism was affected by co-administered antidepressants, drove progressively worse over the course of treatment [11].

Depression and driving performance

Depression alone is likely to affect driving ability and driving related skills. Epidemiological studies show that the use of TCAs significantly increased the risk of becoming involved in traffic accidents [13–14], whereas SSRIs and related compound do not seem to increase traffic accident risks [15]. Nevertheless, Wingen and colleagues [12] did report driving impairment in depressed patients who were treated with SSRIs. They examined on-the-road driving performance of depressed patients who were treated with SSRIs or SNRIs for six to 52 weeks. Wingen and colleagues reported a significantly increased mean SDLP when compared to healthy matched controls. Patients also performed a car following test. When the leading car changed speed, the following car (driven by the depressed patient) had to follow the movement as accurately as possible. Time to adapt speed in depressed patients was significantly increased when compared to matched controls. It has been discussed in this chapter that SSRIs and SNRIs have no significant impairing effect on driving performance. Taking this into account, the authors suggest that the observed driving impairment may be caused by residual depressive symptoms. Future studies in untreated depressed patients should examine whether this likely assumption is indeed correct.

Somnolence and driving impairment

Ramaekers [11] performed a regression analysis to establish the relationship between SDLP differences from placebo and the percentage of patients who reported somnolence. A strong and significant relationship was found ($r = 0.95$), as illustrated in Figure 1.

Figure 1 shows that antidepressants that cause somnolence often affect driving performance in a much more pronounced manner than antidepressants that cause little sedation. Also indicated in Figure 1 is the SDLP increment after having a blood alcohol concentration of 0.05 %, i.e. the legal limit for driving a car in The Netherlands. It is evident that driving impairment of many antidepressants is much more pronounced than that regarded by the law as acceptable for alcohol. Also, various antidepressants cause much more somnolence than observed at the alcohol limit.

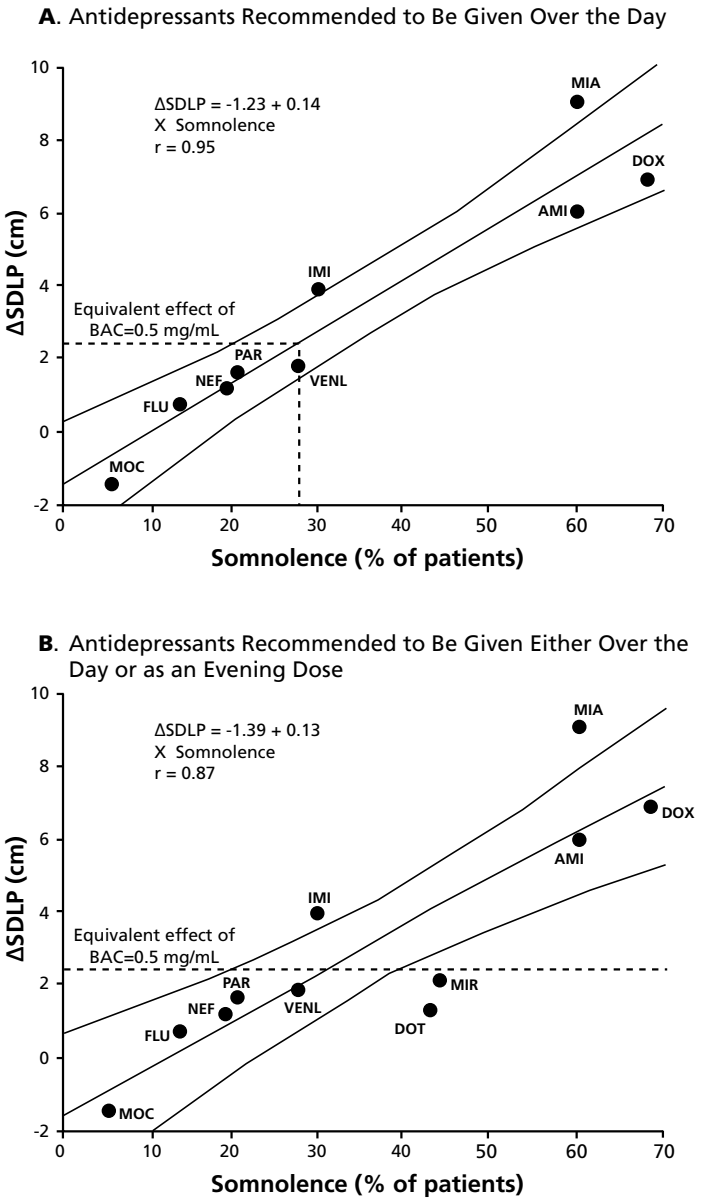

Figure 1 Linear regression (95% confidence interval) between maximum mean ΔSDLP observed for antidepressant drugs in experimental driving studies and the percentage of depressed patients complaining of somnolence. Abbreviations: SDLP = Standard Deviation of Lateral Position, BAC = blood alcohol concentration, MOC = moclobemide, FLU = fluoxetine, NEF = nefazodone, PAR = paroxetine, VENL = venlafaxine, IMI = imipramine, MIR = mirtazapine, DOT = dothiepin, AMI = amitriptyline, DOX = doxepin, MIA = mianserin. (adapted with permission from reference [11]).

Concluding remarks

Driving after intake of TCAs, mianserin or mirtazapine was significantly impaired after treatment initiation. Tolerance developed gradually and, after one week of treatment, driving impairment was absent or much less pronounced. Also, nocturnal drug treatment did not affect next day driving performance. SSRIs and related antidepressants and moclobemide showed no significant effect on driving performance. However, when SSRIs were combined with benzodiazepines with incompatible pharmacokinetic profiles driving performance was significantly impaired. Future studies should be performed in patients focusing on common drug combinations used by people who suffer from depression.

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Attention deficit/hyperactivity disorder (ADHD) and driving safety

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Abstract

This chapter reviews the diagnosis and symptoms of Attention Deficit/Hyperactivity Disorder (ADHD), the extent to which the occurrence of ADHD is related to elevated risk of driving mishaps, a theoretical model concerning how these symptoms and their appropriate medical management impact on driving safety, and both the advantages and disadvantages of ADHD medication management.

What is ADHD?

ADHD is a neuropsychiatric disorder that has high inheritability [1]. It manifests before age six, with symptoms of impulsivity, hyperactivity and inattention significantly beyond what is age appropriate. By definition, these symptoms must impact functioning in at least two realms of one's life, such as home, school, sports, work etc. [1] ADHD is a common developmental disorder, affecting 3% to 8% of children [2], and most (as many as 80%) remain symptomatic into adolescence [4]. The hallmark symptoms – poor sustained attention, distractibility, impaired impulse control and hyperactivity – along with deficits in working memory, impact an adolescent's family life, social relationships, community functioning, and educational success [3]. More specifically, 15% to 20% of children with ADHD develop substance abuse problems, 38% are involved in an adolescent pregnancy, and 32% drop out of high school [4, 5]. ADHD adults are at least 2.5 times more likely to die prematurely from their misadventures than are non ADHD adults [6]. Driving is one domain for which increasing evidence suggests critical, even life-threatening, disruption resulting from ADHD [7–9].

The frequency and costs of adolescent driving mishaps

Motor vehicle collisions are the leading cause of death among adolescents in the United States between 15 to 30 years of age [10]. The U.S. Department of Transportation's Fatality Analysis Reporting System (FARS) reported that in 2003, adolescents accounted for 10% of the U.S. population and 13% of all deaths from motor vehicle collisions [11]. Similarly, in the 30 countries from North America, Europe, and Asia that make up the Organization for Economic Cooperation and Development (OECD) 18–25 year old drivers make up only 10% of the population, but account for over 25% of all traffic deaths [12]. In 2001, motor vehicle collisions accounted for 41% of all deaths among 16- to 17-year-olds, and 38% of all deaths among 18- to 19-year-olds and, in OECD countries, it is estimated that 8500 15–24 year olds die each year in traffic crashes, and in the United States, and across OECD countries [13, 21]. Between 1993 and 2003, total number of driver fatalities for 16- to 19-year-olds increased by 13%, with fatality rate increases of 9% among young males and 25% among young females in the United States [20]. When these deaths are examined by age, gender, and seating position (driver or passenger), 18-year-old male drivers had the highest fatality rate compared to all other groups: 26.2 per 100 000 deaths (Fig. 1) [13].

Similarly, in the United Kingdom in 1994 young male drivers were 4.5 times more likely than 30–59 year old counterparts to be involved in a fatal crash, and by 2002 that figure had risen to seven times more likely [13].

Adolescents' risk for non-fatal collisions is also higher than other age groups. The risk of collisions per mile driven for 16- to 19-year-olds is four times greater than that of older groups, with 16-year-olds having the highest risk [14]. Drivers between

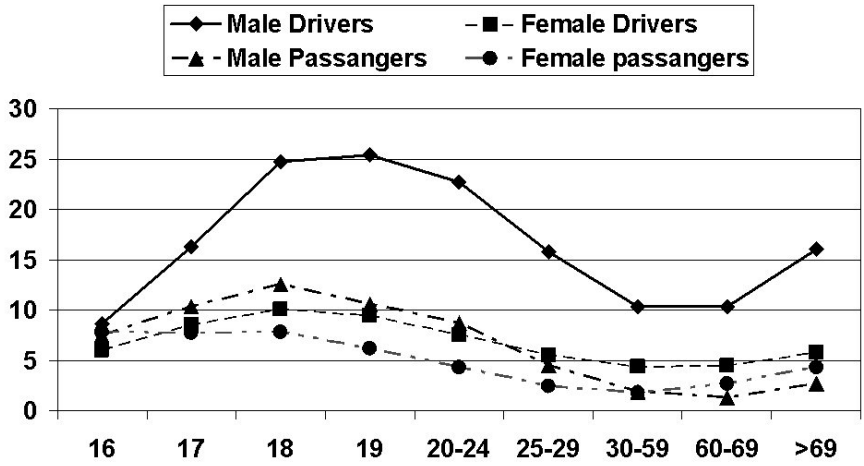

Figure 1 Deaths/100,000 people, reprinted from The Insurance Institute for Highway Safety.

ages 16 and 20 cause over 15% of all auto collisions [11] and, among fatal collisions with passengers of all ages, 20% occur while an adolescent is driving [12].

Several factors have been found to relate or contribute to driving risk for adolescents, some particularly for adolescents with ADHD. In the "100 Car Study," video, GPS, and accelerometer data were collected continuously for 12 months from 100 drivers in the Northern Virginia and Washington DC area. The leading cause of documented driving collisions was driver inattention [15]. Additionally, in 2003, 25% of 15- to 20-year-old drivers killed in collisions had a blood alcohol content of 0.08 g/dl or higher [20], which is significant when considering ADHD drivers may be more impaired at this BAL than non-ADHD drivers,[16] and that individuals with ADHD are more likely to abuse alcohol [17]. The risk of automobile collisions rises with increasing numbers of adolescent passengers, such that mortality rate goes up 130% for each adolescent passenger [14]. Further support for the important point that adolescent drivers are a danger not only to themselves, but to others is provided by one study in the US and the Netherlands which showed that for every 10 young driver deaths in traffic accidents, 13 other passengers or drivers also lost their lives [13]. Finally, fatal collisions involving adolescents are more frequent between Friday and Sunday and between the hours of 21:00 and 6:00 [14]. when ADHD medications are likely not to be taken or when their effects are waning. In Virginia, 40.9% of fatal collisions in 2003 involving those 16 to 20 years of age occurred between 21:00 and 6:00 [21]. For drivers 16 to 20 years of age, 29% of all fatal collisions occur during the summer months of June, July, and August, the months when many ADHD adolescents take "drug holidays" because school is no longer in session.

In summary, automobile fatalities and injuries among adolescents are a huge public health problem. Driving conditions that increase collision risk for adolescent drivers include month of year, day of week, time of day, number of teenage passengers, and use of alcohol while driving. As we addressed briefly above and will demonstrate below, ADHD is a major added risk factor in adolescent and young adult driving mishaps.

The increased risk of driving mishaps among adolescents with ADHD

If the high vehicular collision rate among adolescents and young adults in general is a significant public health concern, there should be even greater concern for adolescents with ADHD who have almost four times as many collisions [18], and are more than three times as likely to suffer associated injuries as drivers without ADHD [19]. An increasing body of research documents this risk among young drivers with ADHD. For example, Fischer et al. (2006) reported that parents of drivers with and without ADHD indicated that ADHD drivers were less likely to use safe driving practices, with nearly 40% of parents of young drivers with ADHD

rating their child as deficient in driving skills (more than 1.5 standard deviations below the mean of the non-ADHD group) [22]. Similarly, a 1995 report by the U.S. Department of Transportation's National Highway Traffic Safety Administration showed that the presence of severe childhood ADHD correlated with significantly greater likelihood of traffic citations in later years, as compared to children with no or only mild ADHD symptoms [20].

In a longitudinal study which followed clinically-referred hyperactive children and community control children for 13 years, a greater percentage of drivers from the hyperactive group reported less-safe driving practices, more traffic citations, more inattentive driving errors on driving simulation evaluation, and more impulsive driving errors during on-road testing [21]. Results of several longitudinal studies that recruited community-based rather than clinic-based samples have matched these findings. Specifically, in a large sample study from New Zealand, young drivers who demonstrated more attention deficits at age 13 had a greater risk for injury during a collision, driving without a license, and traffic violations, even after controlling for confounding factors such as co-morbid conditions, conduct problems, driving experience, and driver's gender [22, 28]. Based on the results of these and similar studies it seems clear that ADHD alone, apart from additional risk attributed to conduct problems and other factors, places drivers at increased risk.

Several studies have also been done investigating specific factors that may affect or relate to the driving risk of young adults with ADHD, including, age, gender and medication usage. We conducted an internet survey in 2006 of 439 drivers with ADHD, half male, a third being adolescents (16–18 years), a third young adults (19–24 years) and a third adult drivers (25–62 years) and looked at the relationship of age and gender to ADHD driving risk [23]. There was no difference in reported driving mishaps between males and females in terms of collision or citations. Interestingly, while there was an increase in driving mishaps going from adolescents to young adults, as expected, there was no drop in either self-reported collisions or citations between young adults and adults. It should be noted that this was self-report data from an open survey where there may have been some unknown biases.

A recent retrospective survey revealed that ADHD drivers taking stimulant medication reported more speeding tickets (4.1 *vs*. 1.4), total citations (11.7 *vs*. 3.9) (both p's $< .001$), and license suspensions (1.7 *vs*. 0.7, $p = .023$) than untreated cases [25]. Unfortunately, while interesting, little can be concluded from these findings since there was no random assignment to medication and drivers with more severe ADHD may have been more likely to receive medication; medication dosing was not controlled; and it was not reported whether the medicated drivers were taking medication on the day of the event or, if so, whether the medication was still active in their bodies at the time of the mishap. An earlier study based on chart reviews of stimulant-treated adults with ADHD reported *improvement* of driving performance during stimulant treatment, but design flaws limited further conclusions [24].

Given these shortcomings of the longitudinal studies cited, and the dangers generally involved in real world cross sectional observation studies, other research methods have been utilized to explore driving difficulties in ADHD. For instance, the use of virtual reality driving simulators in several studies has demonstrated more

impairment among the ADHD participants with hyperactivity, including more variable reaction times, more frequent errors of impulsiveness, greater steering variability, and a greater number of scrapes and collisions of the simulated vehicle [9, 10]. Fischer and colleagues also demonstrated more erratic control of the simulated vehicle and a greater number of scrapes or collisions among adults with ADHD compared to those without ADHD [22].

Finally, while it has been demonstrated that ADHD alone does increase driving risk, it is important to note that individuals with ADHD also carry an increased risk for other comorbid conditions including mood, anxiety, conduct and substance use disorders that may further impair driving performance. While evaluating the effects of two doses of alcohol (0.04 and 0.08 BAC) on the neuropsychological functioning of an ADHD group and a control group of adults, Barkley and colleagues (2006) found that the ADHD group demonstrated significantly greater deterioration in performance, even at the lower dose of alcohol, than did the control group [17, 25]. This suggests that ADHD is not only a risk factor in and of itself, but may also enhance the power of other risk factors.

In summary, several sources, including highway statistics, retrospective and longitudinal studies, and computer-simulated driving studies, illuminate the markedly increased risk for driving fatalities, mishaps, and traffic violations among adolescents and young adults with ADHD. These events most likely result from the attentional impulsive symptoms of ADHD, which can continue into adulthood. There is a pressing need to address and neutralize these elevated ADHD risk factors in order to save lives and avoid life altering injuries that impact not only ADHD drivers, but others on the road with them.

A theoretical model of ADHD increased risk of driving mishaps

In order to effectively address and neutralize increased risk for driving mishaps among ADHD drivers, it is important to identify, understand, and target specific areas contributing to that risk. Michon [26] developed a three-dimensional hierarchical model of driving abilities or competencies for all drivers in which higher level abilities can harness lower levels to serve larger goals. Deficits in abilities lower on the hierarchy may profoundly affect higher-level driving performance, while deficits at higher levels may have little or no influence on lower-level competencies.

Further, the level at which impairments are found may have significant bearing on the type of interventions used to improve driving. The three levels can be understood as: 1) basic perceptual-motor-cognitive abilities (*operational* level), 2) application of these abilities on the road negotiating traffic and street signals (*tactical* level), and 3) judgment employed before and during driving (*strategic* level). *Operational* skills are the native abilities one brings to driving and may be assessed through basic visual and neuropsychological tests; *tactical* skills are acquired

through driver's education and experience, influenced by driver attention, and are assessed through on-road and driving simulation examinations; and *strategic* skills are acquired over time as a function of driving and life experiences. These three levels determine one's driving performance capabilities, which determine one's driving safety, which in turn influence one's risk of driving mishaps. The dramatic reduction in driving collisions/miles driven from ages 16 to 25 in the general population [14] is generally attributed to improvement in tactical and strategic skills through driving experience, whereas the increase in mishaps as drivers reach ages older than 55 is thought to reflect declines at the operational level, such as vision and information processing speed [27, 28].

Individuals with ADHD have been found to have significantly more collisions and moving vehicle violations than their age- and gender-matched peers [22]. They have typically not been found to be deficient in basic perceptual skills, such as visual acuity and depth perception (*italics*, Fig. 2), but may have motor and cognitive deficits in areas such as visual working memory, response inhibition, sustained attention, freedom from distraction, and divided and selective attention [29, 30]. It is speculated that ADHD's core symptoms of inattention, impulsivity and hyperactivity impact all three levels of driving competency (see Fig. 2).

This has been confirmed with neuropsychological and driving simulation studies comparing un-medicated *versus* medicated drivers with ADHD *versus* age-gender matched controls (**bold** items in Figure 2) [19, 37]. It has also been speculated that ADHD is associated with deficits in working memory [31], possibly making

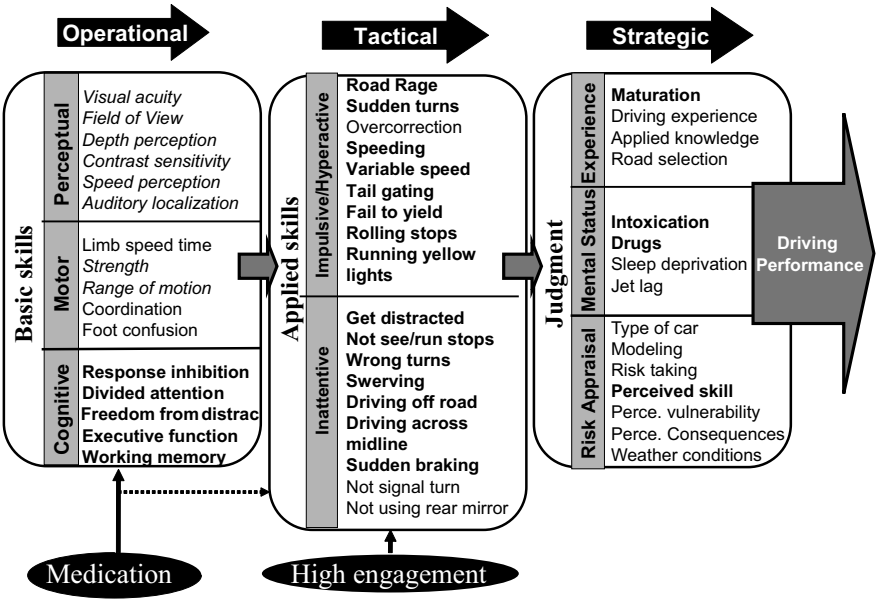

Figure 2 Theoretical model of ADHD driving risk factors; **Bold** are confirmed, *Italic* are unlikely.

it more difficult for individuals with ADHD to learn from experience and benefit optimally from personal or vicarious contingencies. Contrary to the general public, our recent investigation demonstrates that occurrence of driving mishaps does not reduce with age among drivers with ADHD [22].

Given that stimulant medications have been found to improve inattention, impulsivity and hyperactivity [10, 31], along with working memory [31], such medications might reasonably be expected to improve basic *operational* driving performance, thus indirectly (dotted line Figure 2) impacting tactical abilities, thus improving driving performance and reducing driving mishaps among individuals with ADHD. In fact, when ADHD adolescents on methylphenidate (Concerta®), amphetamine (Adderall XR®) and placebo were compared in a double-blind trial, both medications significantly improved working memory and freedom from distraction (operational level) which correlated with improved performance on a driving simulator (tactical level) [32]. Conversely, anything operating directly in-car to help the driver optimize his/her operational abilities would impact at the tactical level.

In summary, driving requires a complex layering of abilities to operate a vehicle safely. The core symptoms of ADHD can potentially negatively impact many of these essential abilities, possibly contributing to increased driving risk among ADHD individuals. To the extent that stimulant medications reduce the core symptoms of ADHD, medications should be (and have been demonstrated to be) beneficial in improving *operational* abilities, while any factors operating during driving that optimize utilization of these operational skills would be considered *tactical* interventions.

The benefits of stimulant medication in improved driving performance

So far, seven controlled studies have directly investigated the effects of stimulant medication on driving performance, three with adolescents [33, 34, 39] and four with adults [10, 26, 32, 35, 37]. Five of the seven used a virtual reality driving simulator, and two utilized on-road testing.

The first, a double-blind, placebo-controlled study compared seven male college students with ADHD who had discontinued medication in high school to six other male students without ADHD on a virtual reality driving simulator after taking either placebo or 10 mg of immediate-release methylphenidate 90 minutes before driving [10]. While the ADHD participants drove more poorly than the control participants on placebo, performance was equivalent on the stimulant.

The second study used a high-fidelity driving simulator to evaluate driving in male high-school students with ADHD who were taking either one dose of extended-release methylphenidate (Concerta®) at 08:00 or immediate-release methylphenidate (Ritalin®) at 08:00, 12:00 and 16:00 [34, 39]. On both medications,

driving examinations occurred at 14:00, 17:00, 20:00, and 23:00. The extended-release methylphenidate (Concerta®) resulted in superior driving performance in general and specifically in the evening (20:00 and 23:00) when compared to the immediate-release methylphenidate (Ritalin®).

The third study compared the driving performance of 12 male adolescents with ADHD after taking either extended-release methylphenidate (Concerta®) at 08:00 or no medication while driving a standard 16-mile rural-highway-urban course in their own car [35]. Raters blind to the medication condition sat in the back seat and assessed driving performance. This study showed that while on stimulant medication, ADHD drivers reduced their inattentive driving errors by approximately 50%. Furthermore, driving improvements significantly correlated with the dosage of Concerta® ($r = 0.60$, $p < .01$).

In a fourth study, Barkley and colleagues evaluated the effects of two single acute doses of MPH (10 mg, 20 mg) on driving in adults with ADHD [26]. Their results suggested improvement in driving performance on a virtual reality simulator and on a continuous performance test as a function of the 20 mg dosage.

A fifth study, with a double-blind, cross-over design, tested 35 ADHD adolescents (19 male and 16 female) sequentially on a driving simulator at 17:00, 20:00 and 23:00 after they had previously taken equivalent doses of extended-release methylphenidate (Concerta®) or an extended-release amphetamine (Adderall XR®) at 08:00 for 5–12 days [33]. Stimulant medications led to superior driving performance overall when compared to testing done on placebo, and Concerta was superior to Adderall XR ($p <= .01$), while methylphenidate was superior to amphetamine ($p = 0.03$).

Fifteen young ADHD adults were compared on a driving simulator after taking either placebo or 50 mg of Adderall XR® for three weeks in a double-blind, cross-over design. Participants were tested at 2, 7 and 12 hours post ingestion of medication. At 12 hours, Adderall XR® was associated with significantly safer driving performance and fewer driving mishaps [36].

Finally, a Dutch study employed a double-blind, cross-over, on-road design to evaluate driving performance of 18 adults with ADHD 1.5 hours after ingesting either placebo or their usual dose of methylphenidate [36]. Using an instrumented car over a 100 km highway, subjects were given instructions to maintain a steady lane position and speed. After taking methylphenidate subjects significantly reduced lane position variability but not speed variability, and reported driving more safely. Interestingly, improvement in lane variability on medication correlated ($r = 0.60$) with baseline depression scores.

Two case reports involved monitoring routine driving for six months of two college students with ADHD [37]. For three months they drove when taking no medication and for three months they drove while taking 72 mg of Concerta daily. On medication the subjects reported taking fewer risks while driving and their in-car video recoded driving mishaps were reduced by 86%.

In summary, research demonstrates that acute stimulant use improves driving performance both on driving simulators and during one-time road testing. However,

there are no investigations available on the mechanisms underlying such benefits. Given these consistent, positive findings concerning the benefits of methylphenidate improving driving performance of adult, and adolescent and adult drivers with ADHD, and no studies suggesting a negative impact of methylphenidate on driving performance, it is interesting to note that some European countries make it illegal for ADHD drivers to operate a vehicle under the influence of methylphenidate. This may be analogous to requiring individuals with myopia not to drive a car while wearing corrective lenses. Ironically, such legislation may actually threaten public health rather than improve it [38].

Limitations of stimulant medication treatment

While medications to treat ADHD, particularly methylphenidate, have been shown to be effective, many adolescents and/or their parents do not want to take medication for a variety of reasons, e.g. hassles securing a monthly prescription, costs, feeling medication reflects a weakness, medications "make me not myself, less fun," use of medications precludes participation in the military, etc. Nonuse/prescription of ADHD medication is especially prevalent among the African-American population [39]. Additionally, minorities are less likely to be prescribed stimulant medications and are less likely to accept stimulant medications if prescribed [40].

Even when adolescents with ADHD are willing to take stimulant medication, adherence to medication regimens is often suboptimal. This was demonstrated by Charach and colleagues, who followed 79 out of 91 participants in a randomized placebo-controlled trial of methylphenidate for over five years [41]. Adherents to stimulant medication regimens showed greater improvement in teacher-reported symptoms. However, adherence levels dropped over the five years of the study. At two years, 41 participants were still adherent and at five years, only 16 participants (<18%) were adherent [46]. Another study with the same participants looked at moderators and mediators to treatment adherence over three years. Younger participants were more likely to be adherent than older participants [42]. This suggests that adolescents of driving age may be at particular risk for non-adherence. Capone and colleagues [43] followed 5659 patients taking extended-release mixed amphetamine salts (MAS-XR), extended-release methylphenidate, long-acting methylphenidate, or atomoxetine for 15 months. Within the first three months of treatment, 50% were no longer refilling their prescriptions and, by the end of the 18-month observation period, an astonishing 80% had dropped out. Even more striking, it did not matter which of the three medications (Concerta, Adderall XR, Strattera) the patients were prescribed; the attrition rates were identical for all three agents [44]. Furthermore, no other parameter seemed to matter; the same dramatic lack of adherence was evident regardless of race, age, gender, or payer source. It appeared to be a function almost solely of the ADHD itself (there was a minor increased attrition in low-income patients). Figure 3 illustrates recent data reflect-

ing prescription refills of 29 213 patients identified as new to brand in the month of September, 2006. A grace period of 30 days was used to determine whether the prescription was refilled each month following initial prescription. The data is based on Verispan's Vector One retail prescription database, and illustrates how refill rates dramatically drop during the 12 months following initial prescription.

We recently completed an internet survey of 379 individuals with ADHD concerning their medication usage. This research indicated that the factor differentiating those individuals who took ADHD medication daily, *vs*. those who did not take medication at all was perceived benefits of the medication. That is, those individuals who attributed significant benefits to taking ADHD medication were more likely to use daily medication [45].

Even when adolescents with ADHD adhere to their medication regimens, the regimens prescribed by treating physicians sometimes do not cover evening and weekend hours when adolescents are most at risk for collisions. In our recent ADHD driving study, only 6 of 37 (19%) participants on stimulant medications upon entering the study were covered during evening and weekend hours (i.e. taking 12 hour medications seven days a week) [33]. Weekend treatment of ADHD continues to be debated. The benefits of weekend drug holidays were supported by a recent study done by Martin et al. [46] which found that weekend holidays help to decrease problems with insomnia and poor appetite without affecting teacher and parent abbreviated Connors scale scores. However, the study did not include measures on accidents or injuries, and participants ranged in age only from six to

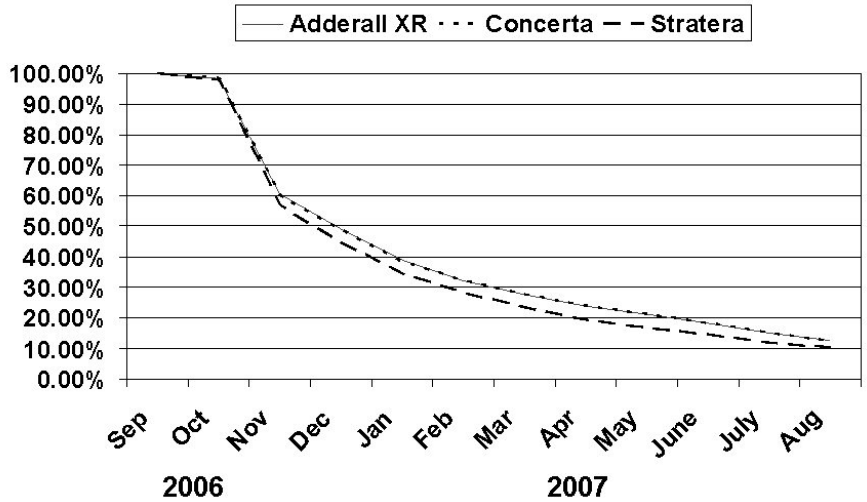

Figure 3 Percent of ADHD patients that remained persistent with prescriptions. This data was provided by Verispan.

14 years. Unfortunately, it is common clinical practice to consider academic and social functioning when choosing stimulant-dosing schedules, without attention to other factors such as driving. Drug holidays are even mentioned in some treatment guidelines as accepted practice, with no discussion about potential hazards in relation to driving or other accidents. In fact, most major ADHD treatment guidelines do not refer to adolescents, and among those which do, driving is never mentioned as a factor to consider in making treatment decisions [47].

Another issue related to the limited medication coverage of adolescents with ADHD is the longstanding belief that children outgrow ADHD symptoms. Even though ADHD symptoms often continue into adolescent and adult years, they are less likely to include overt hyperactivity, and therefore less likely to engender the type of concern that prompts parents to seek treatment from physicians [48]. Adolescents tend to have less obvious problems, such as executive functioning deficits and inattention, which impair driving. However, parents and clinicians are not likely to associate driving concerns with a diagnosis of ADHD. Because of this, adolescent drivers may not have stimulant medications made available to cover all driving activity and to potentially reduce their driving risks. Unfortunately, even when medication is made available, inadequate dosing becomes another significant limitation to effective treatment. The NIH funded Multimodal Treatment of ADHD (MTA) study demonstrated that primary care physicians typically prescribe sub-optimal doses of stimulant medication [49]. Sub-optimal dosing is especially problematic among adolescents who "out grow" their elementary school dose, which may not be increased as the individual ages [49].

A final limitation is medication rebound, which is when symptoms worsen after medication wears off in the evening, compared to symptom base level when medication was never taken. The issue here is whether driving is worse in the evenings when medications wear off compared to if they had never taken medication that day. This is of special concern with driving since there are more collisions and fatalities after 22:00, when rebound may be occurring. The literature indicates that some individuals do demonstrate marked decay during medication "wear off."[50]. Specifically, in one controlled study investigating stimulant medication rebound with long acting stimulants among ADHD adolescent drivers, the amphetamine Adderall XR but not methylphenidate based Concerta, was found to be associated with significant rebound at midnight and 1:00 [51]. Further, there is evidence coming from analogue classroom studies that performance is markedly deteriorated early the morning after having taken any stimulant medication the day before, as compared to taking placebo the day before [52]. While further research is clearly needed to understand the parameters of medication rebound as it relates to driving safety, a "rebound-free" alternative is clearly preferable.

In summary, while stimulant medications have potential benefits to reduce risk of driving collisions and related consequences, there are a multitude of barriers that limit their effective use. A more broadly applicable and embraced alternative or complementary intervention is clearly indicated.

Potential benefits of engagement interventions

An ideal intervention to optimize driving safety of ADHD drivers would be one that: 1) does not rely on driver adherence; 2) works whenever the ADHD driver gets behind the wheel, regardless of time of day, day of week or month of year; 3) both parents and driver can endorse; 4) is appealing to young drivers and does not have any negative social ramifications or other negative "side effects"; 5) does not have an ongoing fiscal cost; 6) does not require continual medical supervision; 7) does not have the potential of being abused or diverted; 8) may discourage driving while intoxicated. If, as research suggests, a major issue for ADHD drivers is inattention to the task of driving, which leads to either failure to anticipate and detect dangerous situations, or late detection demanding sudden adjustments which can look like impulsivity, an engagement intervention that draws the driver's attention back to the process of driving could be hugely advantageous for the ADHD driver. Theoretically there are at least two general ways of re-focusing a driver's attention back onto the process of driving: 1) periodic attention-getting, driving-relevant feedback (e.g. "beeps" when exceeding the speed limit), and 2) attention-demanding, driving-relevant activities (e.g. having to adjust accelerator pressure to maintain constant speed). This is illustrated by a study we conducted comparing driving performance of non-medicated adolescent drivers with ADHD while driving a simulator in the automatic or manual transmission modes [53]. At 20:00 and 23:00 subjects drove the simulator for 15 minutes, once in automatic and once in manual mode in a randomized, counterbalanced manner. It was hypothesized that manual transmission would be more engaging, requiring the driver to coordinate speed, clutch, and gear shift when approaching and leaving intersections in order to avoid the negative feedback of grinding gears. Manual transmission led to greater self-reported attention to driving and improved driving performance similar in effect size to stimulant medications.

Many new "advances" in the automobile industry involve removing the driver from the driving environment by increasing sound attenuation, "smoothing" the ride by softening suspension, adding automated systems that control speed on open roads and decelerate vehicles when approaching objects at dangerously close distances and excessive speeds. While these innovations make the driving experience more comfortable and possibly more appealing to the general public, particularly above a certain age, they come at the cost of allowing the driver to be more disengaged and inattentive to the process of driving. Such "insulating" efforts may be counter-indicated and frankly dangerous for drivers with attentional difficulties. This insulating strategy is in marked contrast to "performance vehicles" that maximize certain types of driver's feedback and give the driver a greater sense of being in control, which may be preferable for ADHD drivers. Fortunately, it may be speculated that maximized feedback from the vehicle (as in a "performance vehicle" or "sports" car) would be more appealing to young drivers in general than a fully automated car, which maximizes the potential for acceptance of an engagement intervention.

In summary, optimizing the driving environment to maximize driving-relevant feedback and activity has the potential of improving attention to the driving process 24/7, thus minimizing the impact of ADHD symptoms and promoting greater driving safety whenever the driver gets behind the wheel.

Adolescents and young adults have an increased rate of driving mishaps, including fatalities and debilitating injuries, making motor vehicle collisions the leading cause of death in this age group. ADHD appears to interfere with all three levels of driving ability (operational, tactical, and strategic) which may account for their further increased risk [19]. Drivers, parents and physicians should be aware of this, and medication usage and adherence should be strongly considered. While stimulant medications have been shown to improve driving performance in controlled studies, there are multiple barriers to their effective, routine use to a degree that might significantly impact driving safety for the ADHD population. In contrast, enhancing engagement of drivers in the process of driving with driving-relevant feedback and activities has both theoretical and practical advantages that might enhance attention to the process of driving, promote safer driving and lead to fewer driving mishaps and therefore negative consequences. Such an intervention would have none of the limitations of medication.

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Drugs, Driving and Traffic Safety
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Drugs, driving and traffic safety in Parkinson's disease

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Abstract

The driving ability of patients with Parkinson's disease may deteriorate due to motor impairment, cognitive deficits, and the side-effects of antiparkinsonian medication. In particular, sudden sleep episodes and daytime sleepiness have been discussed as major problems in the past decade. Although evidence consistently shows that patients' driving ability is impaired and that patients are not able to assess the impairment adequately, studies differ as to the exact influence of the aforementioned factors. This may be explained by various factors which moderate the association between driving ability and disease-related impairments (e.g. the measure of driving ability or the type and difficulty of the test or driving task being undertaken). Thus, even though all the aforementioned factors have been shown to have significant impact on driving performance, they are not sufficient to predict driving ability. Recent research has shown that the ability to compensate for disease-related impairments seems to be a crucial factor, and should be considered a major reason for the large interindividual variation of driving performance even at the same disease stage. Unfortunately, compensatory behaviour is not captured by traditional psychometric tests. Therefore, future studies should put special emphasis on the diagnosis of compensatory behaviour and how to train it. Basically, driving ability has to be assessed individually and must be considered not as a static, but as a dynamic factor which can be preserved and even improved.

Introduction

In the past decade driving ability in patients with Parkinson's disease (PD) has been intensively discussed. A major reason for this was a report on eight patients who caused traffic accidents due to sudden onset of sleep (SOS) while driving, and who were undergoing treatment with the nonergoline dopamine agonists pramipexole or ropinirole [1]. Prior to this report, studies on the subject were rare

and concentrated on the prediction of patients' driving performance by classical motor scales of disease severity [2–7]. However, the report of Frucht et al. [1] triggered a spate of research into patients' driving abilities and the phenomena of SOS and daytime sleepiness in PD. In the following, an overview will be given of the evidence regarding
- impairment of PD patients' driving abilities in general;
- the impact of disease severity/motor symptoms, cognitive deficits and daytime sleepiness;
- patients' self-assessment and compensatory behaviour.

Finally, conclusions will be drawn on the diagnosis of driving ability in PD as well as on possibilities to preserve it.

Impairments of PD patients' driving ability

All studies on the subject have shown the driving ability of PD patients to be impaired. No matter how driving ability was operationalised, patients performed worse than healthy controls. This holds true for patients'
- accident rate [4, 8, 9];
- on-road driving performance [6, 10–15];
- performance in various driving simulators [3, 4, 15–20];
- performance in psychometric tests used to assess driving ability [6, 20].

In an interview study 150 PD patients and 100 healthy controls were compared with respect to their accident rates [4]. Even though patients had not had more accidents over the course of their lifetime, the number of accidents per million vehicle miles of travel for the three years prior to the survey was higher. This was confirmed by another questionnaire survey with 89 PD patients and 423 healthy controls [8]. The authors considered the last five years and found patients' accident risk to be 2.5 times higher than the controls'. We analysed 6620 questionnaires and performed 361 telephone interviews on traffic accidents in PD [9]. The results were that 14.5% of all 5210 licensed patients had been involved in at least one accident during the last five years and 10.8% had caused at least one (these values were 16.5% and 11.7% respectively for the subgroup of active drivers). Italian authors studied 204 patients and reported a markedly higher accident rate of 29% in active drivers [7]. However, they did not specify the period of time to which this portion refers. Unfortunately, no healthy controls were considered in the latter two studies.

Comparing the culpability rates of PD patients with those of the German total population in 2002 revealed that when patients were involved in an accident, 69% of the time it was their fault, compared to only 57% for the corresponding age-group in the German total population [9, 21]. Figure 1 shows these culpability rates for various age-groups.

It is well known that the culpability rate of older drivers increases with age [22]. As Figure 1 shows, this also applies to PD patients. Indeed, the difference between

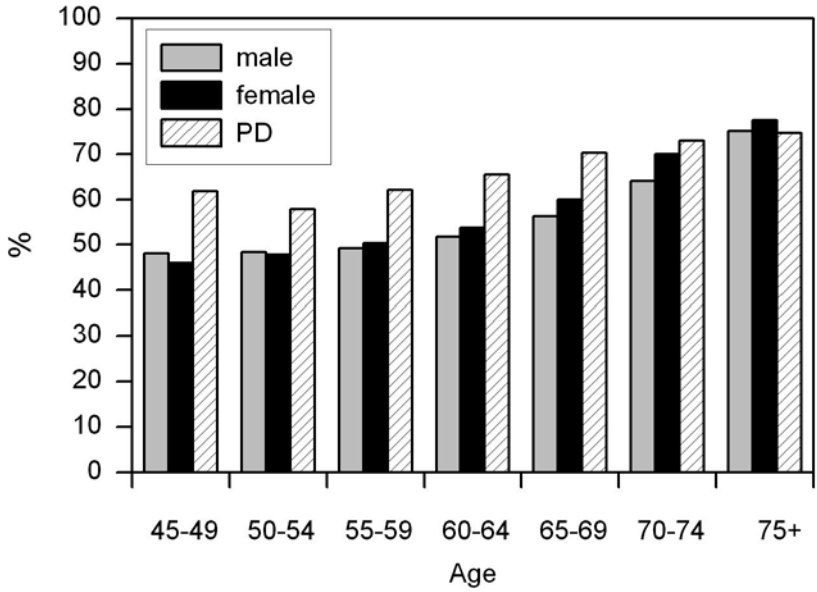

Figure 1 Culpability rate in traffic accidents of 621 PD patients aged 45 + years compared to the German total population in 2002 [9, 21].

PD patients and the total population is especially pronounced for younger age groups, whereas with increasing age the rates converge again.

In interviews about the circumstances of their accidents patients mainly reported typical age-related accidents at crossroads and while parking [9]. Few patients reported accidents due to freezing or blockade-like phenomena [23]. In a review in 2002 the highest prevalence of SOS-related accidents in PD patients reported in any study was only 0.24 % [24]. In our study, 2.2 % of all licensed patients admitted to having had an accident due to SOS, and 8 % of all accidents were associated with SOS. By comparison, 6.5 % of the accidents of the German total population in 2002 were fatigue-related. Since PD patients are likely to avoid typical fatigue-related driving situations such as night-time trips and long distances [4, 8, 10], these figures only partially reflect the severe influence of SOS on driving safety. Additionally, many patients will try to conceal such episodes, fearing the loss of their driving license. Therefore, we must assume a large number of unreported accidents due to both freezing and SOS. In our telephone interviews 17 % of the patients who initially denied having experienced SOS while driving later admitted to having experienced it after all [20].

Throughout all studies with on-road driving tests, PD patients were characterised by more negative global ratings of driving safety and a higher number of errors, critical situations and severe violations of traffic regulations [6, 10–14]. Analogous with their typical traffic accidents (see above) the following situations and driving tasks – known to be especially difficult for older drivers [22] – were found to be even more problematic for PD patients:

– crossroads and intersections (turning left, roundabouts, traffic lights);
– urban areas;
– high traffic density;
– driving in and adapting to traffic flow;
– changing lanes;
– head turning/accounting for the blind spot;
– driving backwards and parking;
– lane-keeping.

Radford et al. [25] examined 51 patients' on-road driving performance and considered 12% of them to be unsafe drivers. Heikkilä et al. [6] reported that 35% of their 20 patients, but none of their 20 controls, were unable to drive. The study of Amick et al. [26] found similar results with 7 of 21 patients being rated as unsafe. Singh et al. [15] based their judgment on a combination of clinical tests, reaction times on a test rig and an on-road test and found 32.5% of 154 patients to be unable to drive. The highest rate of unable drivers was found by Wood et al. [11] who stated that 56% of their 25 patients, but also 24% of their 21 controls, would have failed a state-based driving test. Grace et al. compared 21 PD patients, 20 patients with Alzheimer's disease (AD) and 21 elderly controls, and found AD patients to be more impaired than PD patients [10]: Nine AD patients were judged marginally safe and two AD patients unsafe by a driving instructor, whereas seven PD patients were only marginally safe. The remaining 14 PD patients and all controls were safe. The most extensive on-road tests were performed by Uc et al. [12–14] who tested about 75 PD patients and 150 controls. Patients made more navigation errors and safety errors both with and without distraction by secondary tasks or a route-following task. Unfortunately, the authors did not state how many of their subjects were considered unfit to drive.

Possibly, the very low proportion of unsafe drivers in the Radford study [25] might be explained by the fact that patients were allowed to use their own cars. But certainly, a major source of differences between all these study results is the selection of the test course and the driving tasks. The more situations the test course includes that are specifically difficult for the target group (like complex intersections for older drivers), the more subjects will fail the driving test. This point was also acknowledged by Heikkilä and colleagues [6], who argued that their course was very difficult. In contrast, Uc et al. [13] suppose that they could have found more pronounced effects with respect to the influence of distraction if they had chosen a more challenging route.

Studies using driving simulators of different complexity demonstrated substantial PD-related impairments. In their early publications Madeley et al. [3] considered 10 patients *vs*. 20 controls, and Lings and Dupont [5] tested 28 patients *vs*. 109 controls in quite simple driving simulators (single PC, simple controls). Zesiewicz et al. [16] investigated 39 patients and 25 healthy controls but did not specify the features of the simulator they used. Similarly, Singh et al. [15] reported only that they had tested 135 patients in a "static driving rig" to measure reaction times for braking. Stolwyk et al. [17–19] gathered data from 18 patients and 18 controls in

a fixed base simulator with a real car as mock-up and a single display monitor. We tested 24 PD patients and 24 healthy controls in a motion-based simulator with a real car as mock-up and a 180 degree horizontal field of view [20]. All these studies showed that patients reacted more slowly and performed braking manoeuvres more inaccurately, disregarded red traffic signs more often, had more collisions and committed more errors than controls. As in on-road tests, patients had major difficulties in lane keeping.

Although these simulator studies seem to generally give the same results, they vary significantly in details. Again, a major source of differences is the selection of traffic situations with which the patients must cope. Thus, all reported simulator studies are basically characterised by using only a small subset of driving tasks, mostly concentrating on psychomotor driving skills (e.g., lane-keeping, braking). In contrast, we designed a representative test course with a series of traffic situations comparable to a driving test in real traffic [20]. Overall, 21 % of our patients and none of our controls displayed questionable driving ability. Further analyses showed that PD patients committed significantly more driving errors than controls – mainly due to going off the road, false indicating behaviour, driving too slowly and endangering others. Patients' bad lane keeping performance was also seen in an increased standard deviation of lane position (SDLP). However, in a special driving scenario where a sudden braking manoeuvre was necessary, we could confirm neither an increased reaction time nor an increased rate of collision as compared to healthy controls. Probably this scenario, featuring a car in front braking very unexpectedly, was too difficult for both our patients *and* our controls, resulting in a ceiling effect. This is an essential point which has to be considered in any study using driving simulation: all parameters strongly depend upon the design of the scenario in which they are measured. In fact, any driver can be caused to have a collision in a simulator. Thus, a major failing of many simulator studies is that the scenarios are neither specified nor theoretically-based. In particular, this holds true for the study of Zesiewicz et al. [16] whose primary outcome measure was the number of patients *vs*. controls who had at least one collision during their test. Without knowing the kind of scenario in which the collision occurred and with no information about the type of collision, the validity of such a study's results for real driving can not be assessed. There is a substantial difference between collisions resulting from badly-tuned brakes as compared to collisions resulting from an extreme delay of the braking response after having perceived an obstacle.

Another important source of differences between both the simulator and the on-road studies concerns the selection of subjects. The simulator study of Lings and Dupont [5] is open to criticism in this regard, since patients had been included who had quit driving, or who had never even acquired a driving license. However, the authors argued that they had also performed all analyses without these patients and did not find different results. Whilst 18 % of the patients of Zesiewicz et al. [16] had quit driving, the research groups of Madeley [3] and Stolwyk [17, 18] only considered active drivers, as did we in our study [20]. Furthermore, studies differ strongly in their inclusion criteria with respect to dementia. For example, Wood et al. [11] tolerated MMSE scores [27] as low as 24, and found more than half of their patients

to be unsafe drivers. In our study we only included patients with a score of at least 27, and found only a fifth of them to have questionable driving ability. However, as discussed in the section after the next, not all studies could find a significant correlation between driving performance and MMSE as a global indicator of cognition.

Lastly, studies using psychometric tests to investigate driving-related functions separately also showed PD patients to be impaired. However, appropriate results will be discussed in the section after next, which deals with the predictability of driving performance by cognitive deficits as examined by neuropsychological measures.

Taking together the results from on-road and simulator studies, impaired driving is a common problem for PD patients. However, the proportion of unable drivers ranges from 12 to 56% depending on (a) the inclusion criteria, (b) the selection of driving tasks and (c) the selection of criteria for safe driving. As a consequence, the diagnosis of driving ability must be performed on an individual level, as consistently stressed by all authors on the subject.

The impact of disease severity as measured by classical motor scales

Whereas all publications provided consistent evidence that PD patients' driving ability is impaired, the relation of disease severity to safe driving is still unclear. Indeed, most of the studies on the subject set out to correlate driving ability to the scales commonly used to assess PD related motor impairment, but not all authors could confirm a significant association [5, 6, 11, 14, 20 *vs*. 3, 4, 8, 15, 16, 25].

According to Adler and collegues [8] the presence of motor impairment significantly predicted patients' accident rate over the last five years. The accident risk of patients with motor impairment was 3.2 times higher than that of patients without motor impairment. Unfortunately, the authors did not specify their measure of motor impairment. Dubinsky et al. [4] used the Hoehn and Yahr scale [28] and also found patients' accident risk to be associated with the degree of their motor impairment: the number of accidents per million vehicle miles of travel in the last three years was significantly higher in patients of the Hoehn and Yahr stage 3 than in controls and patients of stage 1. The accident risk of patients in stage 2 was only descriptively higher than that of controls, while the accident risk of patients in stage 1 was actually lower than that of controls. Furthermore, in stage 3 the accident rate was significantly higher than the rate for the states of Kansas and Missouri and the nationwide rate for drivers older than 55 years. However, this correlation could be confirmed neither for the NUDS [29] nor for the Schwab and England activities of daily living score [30]. Nevertheless, those authors did not consider the Hoehn and Yahr scale sufficiently sensitive to determine patients' driving ability either, emphasising that some patients of stage 3 can still drive safely. According to Grace et al. [10] the Hoehn and Yahr scale differentiated between safe and marginally safe PD drivers in an on-road test, but only few items of the UPDRS motor scale

(postural stability, speech, facial expression, neck rigidity) [31] did. In the study of Radford and colleagues [25], patients who were rated as unsafe drivers by a driving instructor were significantly more disabled on the Webster scale [32] than those who were found to drive safely. In the driving simulation study of Madeley et al. [3] the ratings on this scale correlated significantly with patients' lane keeping performance and their reaction time. But again, the authors emphasised that disease severity is not sufficient to assess individual patients' driving ability. Zesiewicz and coworkers [16] used the UPDRS motor scale and the Hoehn and Yahr scale, and the occurrence of collisions in their simulator was significantly associated with both scales. Twenty percent of the controls, 20 % of the patients in Hoehn and Yahr stage 1, 56 % of the patients in stage 2, 90 % of the patients in stage 3 and all patients in stage 4 had at least one collision. Finally, in the large sample of Singh et al. 3 % of the patients in Hoehn and Yahr 1, 24 % in Hoehn and Yahr 2 and 88 % of those in stage 3 were assessed as unable to drive [15].

However, as already mentioned, a range of studies were unable to confirm any correlation between patients' disease severity and their driving ability. This holds true for various parameters in the simulator studies of Lings and Dupont [5] and Stolwyk et al. [17] who used the Webster scale and the UPDRS motor scale respectively. In the on-road test of Wood et al. [11], neither the Hoehn and Yahr stage nor the UPDRS motor scale correlated with patients' driving performance, but disease duration did. Heikkilä et al. [6] found patients' on-road driving performance to correlate neither with their Hoehn and Yahr stage nor with their disease duration. Similarly, navigation and safety errors were not associated with disease severity in the experimental drive performed by Uc et al. [14].

The results of our own studies reflect this inconsistent pattern. In the questionnaire data, patients' self-assessment of their motor impairment according to the Hoehn and Yahr scale was significantly associated with their accident rate [9, 33]. However, with an average of about 1.5 the corresponding odds ratios should be considered rather small – especially in a sample of more than 5000 patients. In our simulator study the total number of registered errors was associated neither with patients' Hoehn and Yahr stage, their UPDRS motor score nor with their disease duration [20]. But in some of our scenarios patients' Hoehn and Yahr stage had a significant impact on their lane keeping performance, depending on the difficulty of the driving task: SDLP was only increased for Hoehn and Yahr stage 3, but not for the lower stages if the scenario was easy. But with increasing task difficulty the differences between the stages and eventually even the difference between patients and controls disappeared.

Both in on-road and simulator studies the comparability of correlations between motor impairment and driving ability is strongly influenced by methodological issues. In addition to use of different scales to assess disease severity and different methods to assess driving performance, inclusion criteria also vary from one study to the next. For example, some authors include only active drivers and control patients for dementia, while others do not (see above). Considering that the decision to quit driving as well as the appearance of dementia are associated with both disease severity and disease duration [9, 34], a large source of confounding becomes evident.

Additionally, the correlation between driving performance and motor impairment directly depends on the selection of driving tasks and criteria. These moderating variables might explain the contradictory findings of previous studies. For example, Madeley et al. [3] considered lane keeping performance and reaction time in a rather simple simulator and the analyses of these specific parameters yielded a significant impact of disease severity. In contrast, Stolwyk et al. [17] had a more advanced simulator and could not confirm an association between disease severity and lane keeping performance in a quite difficult lane tracking task. Our results agree with both of these studies, as we found a significant association between SDLP and disease severity only in easier and not in more difficult scenarios.

Other authors like Wood et al. [11] or Heikkilä et al. [6] considered less specific parameters as indicators of driving safety. Thus, they could not confirm a significant association between disease severity and a global rating of driving safety after an on-road test. This is consistent with our finding [20] and that of Uc et al. [14] that the number of driving errors (as a rather global measure) did not significantly depend on disease severity.

To summarise, only very specific indicators of driving safety can be predicted by classical motor scales of disease severity – primarily, indicators relating to psychomotor skills like lane keeping performance or reaction time in driving tasks of minor or moderate difficulty. The more complex the driving task and the parameters involved, the less likely a significant correlation with disease severity will be found. Therefore, studies which assess driving performance by an overall rating of an experimental drive with varying scenarios are less likely to detect significant correlations with motor scales. Consequently, disease severity as measured by classical motor scales has to be considered insufficient for predicting a patient's driving ability.

The impact of cognitive impairments and psychometric tests

In neuropsychology it is well known that PD is associated with deficits in executive and visuo-spatial functions as well as dementia [see 35 and 36 for a detailed overview]. But like motor impairment, evidence about the impact of PD related cognitive deficits on driving performance is not consistent either. While Dubinsky and colleagues [4] found the accident rate over the past three years to be significantly increased in patients with an MMSE score below 27, a score below 25 did not predict the accident rate over the last five years in the study of Adler and collegues [8]. Likewise, the number of collisions in the driving simulator study of Zesiewicz et al. [16] correlated weakly with subjects' MMSE scores in tendency ($r = 0.30$), but various parameters of driving performance considered by Stolwyk et al. did not [19]. Heikkilä et al. [6] reported that patients' on-road performance was not associated with their MMSE score. Grace et al. [10] also showed that PD drivers rated as safe did not differ in their scores from those rated as marginally safe. In contrast, Uc et al. [14] found the score to be associated with both navigation and safety errors while performing a route-following task.

Several authors have applied more sophisticated batteries of neuropsychological tests [10, 12–14, 19, 25, 37]. However, the various papers strongly differ in the conclusions they draw with respect to the impact of cognitive deficits on PD patients' driving performance. For example, according to Radford et al. [25] patients who were rated as safe drivers did not differ from patients who were rated as unsafe drivers in the majority of cognitive parameters. Thus, authors concluded that cognitive abilities are minor predictors of PD patients' driving fitness. In contrast, Stolwyk et al. [19] concluded that although PD is primarily considered a movement disorder, the cognitive symptoms of PD appear to have a strong effect on driving performance. Likewise, Uc et al. [14] found that driving performance depended rather on cognitive and visual aspects than on motor impairment. However, with respect to their data [12–14], one has to keep in mind that they considered safety errors when cognitive load was heightened by a secondary task. Another problem in the comparison of all these studies is that they strongly differed with respect to the tests which were included in the batteries. Most commonly used was the Trailmaking Test [38], for which significant correlations with driving performance were found in all [10, 12–14, 16, 19] but one [37] of the studies employing it. Specifically, correlations existed either for the performance in the B part of the test as a measure of psychomotor speed, visual search and executive function, or for the difference between parts B and A as a measure of cognitive flexibility independent of motor functions.

So far, two studies have applied a specific battery of tests which is traditionally used to examine driving ability [6, 20]. In fact, these tests are acknowledged by law to assess driving ability in Germany and Austria and aim at evaluating orientation, concentration, attention, reaction and the capacity to work under pressure [39]. In one of the studies patients' driving ability was assessed by a neurologist, a psychologist and a driving instructor [6]. The judgement of the psychologist (based on the aforementioned battery of tests) correlated significantly with the judgement of the driving instructor (based on an on-road test). Thus, the judgement of the psychologist was much better as an indicator of driving ability than that of the neurologist (based on clinical features of the disease). Overall, authors found both cognitive and psychomotor impairment in their patients while most of the parameters correlated significantly with their on-road driving performance [6]. However, in our study patients generally worked more slowly and with more delays, which seemed rather due to a motor than due to a cognitive slowdown [20]. What is more, we found that the tests were much too difficult for all persons of this age group. When applying commonly-used criteria as regards the failure of the battery, almost none would have passed – neither patients nor controls – even though only a fifth of the patients and none of the controls displayed questionable driving ability in an extensive test in the simulator (see above).

A comparison of all the studies on the subject is problematic not only because of the differences in the batteries of tests but also, again, because of different inclusion criteria with respect to dementia. For example, Uc et al. [14] and Heikkilä et al. [6] considered patients with MMSE scores of up to 22 and 25 respectively, and found cognitive test performance to be strongly correlated with driving performance. In

contrast, we only included definitely non-demented patients with a score of at least 27, and these patients did not seem to be cognitively impaired [20]. Another problem is that many of the applied tests intended to prove mere cognitive factors nevertheless require a motor performance (e.g. pressing a button as fast as possible). In PD especially, it is likely that motor and cognitive aspects are confounded [20].

Finally, two major problems have to be stated with respect to the predictability of driving performance by psychometric tests. First, in our study as in others [e.g. 40, 41], it has been found that age- and disease-related impairments, as measured by psychometric tests, do not affect driving performance as much as one would have expected. Consequently, the validity of psychometric tests to assess the driving ability of older persons and neurological patients is increasingly doubted in the literature. A particular criticism is that traditional tests can not capture the ability to compensate for age- and disease-related impairments – an ability increasingly acknowledged to be an essential factor in the driving ability of these persons (see the section after next). A second major problem is that there is still no driver model which has attained wide acknowledgement and which allows drawing driving ability-related conclusions from isolated neuropsychological functions.

Overall, neither cognitive tests nor psychomotor tests alone proved to be sufficient for predicting a patient's driving ability. Only the MMSE and the Trailmaking Test seem to be useful screening tools. PD patients with severe cognitive deficits – that is, with dementia – have to be considered as unfit to drive [15, 20]. As regards cognitive deficits in non-demented patients, further studies are needed to draw reliable conclusions. Here, we suggest strictly excluding patients at risk of dementia, i.e. with a MMSE score below 27 and – as also suggested by Grace et al. [10] – to stratify patients according to cognitive deficits as measured in psychometric tests (with *vs*. without).

The impact of daytime sleepiness and antiparkinsonian medication

It was not until the report of sleep attacks by Frucht et al. [1] that daytime sleepiness and SOS were extensively discussed with respect to their impact on patients' driving ability. In reaction to their findings, a large number of studies were performed, the majority of them aiming at prevalence estimates and the identification of risk factors. With respect to SOS at the wheel these estimates ranged from 1 % to 28 % [9, 42–46]. Since the episodes reported by Frucht et al. [1] happened while patients were treated with pramipexole or ropinirole, SOS was initially supposed to be a side-effect of these nonergoline dopamine agonists. However, studies showed that SOS also appeared under both ergoline dopamine agonists and monotherapy with levodopa [47, 48]. Furthermore, other factors such as sleep disorders and disease severity seem to be at least as predictive as any type of medication [33]. Thus, most authors now agree that SOS is a multifactorial phenomenon and an expression of

a strongly heightened daytime sleepiness. In contrast, "sleep attacks" in their basic meaning (i.e. without any prior sleepiness) are considered to be rare.

Three studies have explicitly dealt with the impact of daytime sleepiness on driving performance so far [20, 26, 49]. Möller et al. found deficits in the lane keeping performance of six PD patients suffering from SOS in a driving simulator [49], but considered neither healthy controls nor patients without SOS. Recently, Amick et al. could not find any difference in the on-road driving performance of patients with and without excessive daytime sleepiness [26] In contrast, our questionnaire data indicated a heightened accident risk for patients with daytime sleepiness and SOS – even if risks were stratified for disease severity [9]. Equally, increased daytime sleepiness predicted higher speed variability in patients who performed a route-following task in real traffic, indicating worse control of the vehicle compared to healthy controls [13]. In the simulator study we stratified our sample of PD patients according to disease severity (Hoehn and Yahr stages 1–3) as well as according to daytime sleepiness (yes–no) [20]. We compared them with a group of healthy controls both in a representative test course and in a simulation of an extremely monotonous long-lasting night-time trip. While we found only a slight impairment in patients with daytime sleepiness in the scenarios of the representative course, they performed clearly worse in the night-time trip. Lane-keeping performance worsened over the duration of the trip for all subjects, but most strongly for patients with daytime sleepiness. Furthermore, these patients tended to have more critical situations with respect to oncoming traffic due to leaving their lane.

These results provide strong evidence that the correlation between disease-related impairment and driving performance is moderated mainly by type and duration of the driving task. This might also explain why Amick et al. [26] could not find an impact of daytime sleepiness on driving performance whereas Uc et al. [13] did. As Amick et al. [26] stated, measuring driving performance by expert ratings of a driving instructor might be contraindicated when exploring the relationship between sleepiness and driving. The test situation of being observed and assessed may lead to a strongly activating effect in the subjects. In contrast, the experimental drive of Uc et al. [13] lasted about 45 minutes and was quite easy. Most of the time subjects drove on a straightaway four-lane interstate freeway segment. Thus, the more monotonous a drive is designed to be, the more likely it is to provoke sleepiness and associated deficits in driving performance.

Self-assessment and compensatory behaviour

Unlike the impact of the factors discussed above, the evidence as to PD patients' self-assessment of their driving ability is very consistent. It was found in all studies that patients are not able to judge their driving performance adequately, but rather tend to overestimate it [6, 11, 16, 20]. For example, in the study of Heikkilä et al. [6], none of the patients who were judged unable to drive by the driving instructor doubted their own driving ability – all rated it as highly as patients who were

judged to be fit to drive. Similarly, neither the number of collisions in the Zesiewicz study [16] nor the driver safety ratings of the driving instructor in the Wood study [11] correlated with patients' self-assessment. Finally, in our simulator study patients rated their driving performance as highly as the controls, even though they clearly performed worse [20]. In addition, three of the five patients whose driving ability was questionable still considered their performance as average.

In contrast to the self-assessment of driving performance, PD patients are quite able to assess their sleepiness. During the night-time trip in our simulation study, subjective judgements of sleepiness proved to be more adequate than those of the controls [20]. Regardless of whether patients suffered from sleepiness or not, they did not fall asleep more often during the trip than controls did. This was probably due to the fact that patients took advantage of the option to take a break significantly more often (see below).

It is widely acknowledged in the literature that compensatory behaviour is a crucial factor in the driving ability of older people [e.g. 50]. With respect to PD there is also some evidence suggesting its importance. Subjectively, as compared to controls, patients described themselves as driving less often, more slowly and as avoiding difficult conditions (rush-hour, night-time trips, etc.) [4, 8, 10]. This was confirmed by both simulator and on-road tests, as patients drove more slowly than controls, overtook less often and preferred larger distances to cars ahead or strictly avoided car-following situations [5, 13, 14, 17–20]. As previously reported by Stolwyk et al. [18], patients also seemed to sacrifice performance of a secondary task in favour of the driving task in our simulated night-time trip [20].

The ability to allocate resources to the main task and to successfully compensate for deficits was also proved directly in our simulator study [20]. To measure compensation, a part of the simulator trip was repeated under time pressure to impede compensation by speed reduction. The compensatory potential was measured by comparing the conditions with and without time pressure. In the night-time trip compensation was operationalised by the option of taking breaks to prevent sleep episodes. The instruction of time pressure led to a higher average speed and an increase in driving errors both for controls and – more drastically – for patients. In particular, the lane-keeping performance of patients in the Hoehn and Yahr stage 2 worsened. The number of errors (especially those due to going off the lane) correlated with the Hoehn and Yahr stage, the UPDRS motor score and disease duration only in the trip under time pressure, i.e. if compensation was impeded. Thus, it could be clearly confirmed that drivers with PD are able to compensate successfully, especially for the Hoehn and Yahr stage 2. The same effect occurred in the night-time trip: patients made use of the option to take a break significantly more frequently, and in consequence did not fall asleep more often than controls.

Another result supporting the importance of compensation was found with respect to the battery of tests traditionally used to assess driving ability. Indeed, as already mentioned, almost none of our subjects would have passed – neither patients nor controls. By contrast, only 21 % of the patients and none of the controls displayed questionable driving ability in the simulator. This discrepancy also suggested that PD patients' ability to compensate is an important moderator of the association between disease-related impairments and actual driving performance.

Conclusions

All studies demonstrate large interindividual differences in the driving ability of PD patients, making it necessary to assess their performances on an individual basis. Disease severity, cognitive deficits and daytime sleepiness have significant impacts on driving performance. Diagnosis of driving ability has to make use of procedures and tools which are able to trigger the respective behaviour and its impairment. None of the available tools – on-road and simulator driving, psychomotor and cognitive testing – are sufficient to predict driving ability alone. Therefore, a multifaceted approach must be chosen and adapted to the individual patient. In addition to the traditional factors, the ability to compensate for impairment has been proven to be a crucial dimension in driving ability, and should be seen as an indispensable part of diagnosis in the future. Therefore, procedures not only to diagnose but also to train the ability to compensate for disease-related impairment must be developed urgently. Additionally, we suggest applying provocative methods which are specifically adapted to the nature of impairments associated with PD (e.g. monotony to address sleepiness, time pressure to impede compensation by speed reduction). Of course, such methods can hardly be applied in real traffic. Here, driving simulation – especially with regard to the technical possibilities now available [51] – is a very promising tool.

For diagnosis, we recommend a stepwise assessment of driving ability in PD:

1. Exclusion of dementia;
2. Assessment of disease severity and identification of appropriate compensatory abilities;
3. Examination with respect to daytime sleepiness and appropriate compensatory strategies;
4. Exploration with respect to an adequate self-assessment, capacity of self-criticism and a sense of responsibility.

Regarding cognitive deficits in non-demented patients, further studies are needed with respect to appropriate psychometric tests and compensatory potential.

The technique of measuring compensatory potential by provocative procedures will also be useful for patients with other (neurological) diseases and older drivers in general. The same holds true for appropriate driver training schemes. Driving performance of these persons can be substantially improved if they are trained in self-assessment and get the chance to exercise compensatory strategies.

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Drugs, Driving and Traffic Safety
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Drugs, driving and traffic safety in multiple sclerosis

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Abstract

Up to 65% of patients with multiple sclerosis (MS) show sensory-motor deficits and cognitive impairment which influence activities of daily life and driving skills. Although there is certain evidence of driving difficulties among people with MS, only few studies have focused on this problem. Governmental regulations are based on little evidence.

All studies, mostly based on a small number of participants, have revealed that not physical disabilities but cognitive impairment has a strong impact on driving skills., Questionnaires, computer-based neuropsychological tests, and driving simulators have been used in order to assess driving skills. On-road tests have been applied, especially in cases of ambiguous test results.

Certain drugs recommended for different symptoms (spasticity, paroxysmal symptoms) are apt to cause fatigue and sleepiness. Disease modifying therapy (especially intramuscular interferon ß-1a) has demonstrated a beneficial effect on neuropsychological performance that can also improve driving abilities.

Introduction

Patients with multiple sclerosis (MS) show sensory-motor deficits and cognitive impairment in up to 65% of cases [1, 2]. These impairments may influence activities of daily life, including driving skills. In diseases such as stroke, dementia, obstructive apnea and brain injury, decreased attentional and visual perceptual skills, reduced information processing speed, and executive dysfunction have been shown to be related to impaired driving performance [3–10]. Driving is critical for independence and employment opportunities for people with diseases and handicaps. In a 10-year historical cohort register-study on 197 patients and 545 controls, Lings [11] describes drivers with MS as being treated more often at emergency departments than healthy controls after being involved in road traffic accidents.

Although there is evidence of driving difficulties among people with MS, only few studies have concentrated on this problem [5, 12, 13, 14]. These studies have

concluded that neuropsychological assessment might provide prediction of driving skills. An on-road evaluation should be used in cases of ambiguous test findings. Despite the importance of the topic, governmental regulations are based on very little evidence.

Most countries have restrictions on driving permission for handicapped people (cf. *Drugs, Driving and the Law*, by R. E. Mann, in this book). German regulations on acquiring a driving license [15] declare that driving is not possible if a relevant physical handicap, decreased vision, or psychosyndromes exist that influence an individual's discernment. Driving is also restricted in the event of daytime sleepiness (which may interfere with fatigue in multiple sclerosis). Examinations by neurologists can be ordered by legal authorities. Patients may be fit to drive after successful therapy of disease symptoms. In the UK, people with multiple sclerosis are required to inform the Driver and Vehicle Licensing Agency (DVLA) about their diagnosis. Though the DVLA is ultimately responsible for any decision concerning fitness to drive, they may seek advice from specialists – usually neurologists.

In expert opinion, the question of whether physical impairment or the presence of cognitive impairment influences driving ability with MS is being debated [5, 14, 16, 17].

Tools to assess driving in multiple sclerosis

Disease severity

Disability in MS is mainly assessed by the Expanded Disability Status Scale (EDSS). As an ordinal scale it is heavily biased toward locomotor function [18]. Examination by the MS Functional Composite (MSFC) yields a score that exhibits concurrent and predictive validity as compared to the EDSS [19] and includes information about cognition. It is based on the following three clinical dimensions: arm/hand function (Nine-Hole-Peg Test, 9-HPT), ambulation (25-foot Timed Walk Test, T25W) and cognition (2'' or 3" version of the Paced Auditory Serial Addition Test PASAT).

Questionnaires concerning driving abilities

Chipcahse et al. [20] sent a questionnaire on driving to 192 people with MS and 192 controls who were relatives or close friends of the individuals with MS. Ability to drive in MS patients was more often affected by fatigue, leg problems, numbness and eye problems than controls. MS patients reported that they could only cover shorter distances and could only drive for a shorter amount of time as compared to controls. Fatigue was stated to significantly influence their ability to drive, so that their driving plans were affected by fatigue. But fatigue was not the only factor affecting driving skills in MS.

Neuropsychological testing and the driving simulator

There are different instruments in each study, usually based on the common instruments used at the investigating study centre.

Schultheis et al. [5] used two computerized driving tests: the Useful Field of Vision (UFOV) and the Neurocognitive Driving Test (NDT). Prior to their examinations by these tests, patients had to pass a battery of tests that screened cognitive deficits: Block Design and Digit Symbol subsets of the Wechsler Adult Intelligence Scale – Revised, the Motor Free Visual Perception Test – Revised, the Stroop Color/Word Test, the Trail Making Test, and the Paced Auditory Serial Addition Test. The 9-Hole Peg Test and the Ambulation Index of the MSFC were added. The Snell Visual Eye Examination was also administered. Based on these tests, 28 MS subjects were divided into subgroups with (MS+, n=13) and without (MS–, n=15) cognitive impairment. The MS+ group revealed significantly worse results in several driving-specific functions of the NDT and demonstrated poorer performance on two of three subtests of the UFOV.

Lincoln et al. [14] used the Stroke Drivers Screening Assessment, the PASAT, the Stroop test, a test of motor impersistence, Adult Memory and Information Processing Battery Form 2 (tests of memory and IP) in 34 MS patients. In addition, the Extended Activity of Daily Living scale was administered as a measure of functional independence in instrumental activities of daily life.

In a preliminary study Kotterba et al. [17] used a driving simulator *(CAR® Fig. 1)*. Patients had to drive in this simulator in a highway situation for 60 minutes, with a mean speed of 100 km/h, while being presented with different weather conditions

Figure 1 Driving simulator C.A.R.®.

and obstacles. Results of the driving simulator performance were compared with physical and cognitive functions as measured by the EDSS and MSFC in 31 patients suffering from a relapsing remitting form of multiple sclerosis (RRMS). The CAR® was used in cooperation with the German traffic board (Deutscher Verkehrsrat).

RRMS patients showed an increase in the number of accidents and errors in concentration in the driving simulator as compared to the control group of 10 healthy volunteers. In the investigated RRMS patients the degree of physical disability was low, cognitive deficits (PASAT, assessing the working memory as a part of cognition) were prominent. The correlation between accident rate in the driving simulator and PASAT results was significant; no correlation was evaluated between T25 W and 9-HPT. Accidents, therefore, seemed more influenced by cognitive decline than by physical impairment.

In a second study evaluating the effect of interferon ß-1a [21] the accident rate was increased in 24 RRMS patients as compared to 22 healthy individuals (3.4 ± 3.4 *vs*. 2.9 ± 2.9) before the beginning of the therapy. Driving performance improved during 24 months of IFNβ-1a therapy. Significant changes were shown in patients, ending up with results equivalent to controls at month 24 (1.1 ± 1.4 *vs*. 1.1 ± 1.4 accidents in control group). Errors in concentration were initially more frequent in patients with RRMS (16.5 ± 15.1 *vs*. 11.4 ± 8.7); however, after 24 months of IFNβ-1a treatment, the rate equalized in both groups (5.9 ± 3.7 *vs*. 5.1 ± 4.9). Improvement in PASAT scores and reduction of errors in concentration were significantly correlated.

On-road tests

Only few studies have compared results of neuropsychological tests to on-road driving ability in people with MS.

Shanke et al. [22] tested 33 MS patients with a neuropsychological battery, on the basis of which some drivers were sent on an evaluation on public roads. Fourteen drivers were found to be unfit to drive. Multiple regression analysis indicated that cognitive skills, reaction time, and insight into their illness were the strongest determining factors in obtaining a driving licence.

In a subsequent study Schultheiss et al. [23] performed a follow-up observation on 13 MS patients with- and on 14 MS patients without cognitive deficits, and also on the 17 healthy controls investigated in the first study. Those patients with known cognitive impairment had significantly more motor vehicle accidents.

After neuropsychological evaluation, 29 participations in the study by Lincoln et al. [14] were assessed on the road by an approved driving instructor who was blind to the outcome of cognitive testing. Seven failed and 21 passed the on-road assessment. Tests which differed significantly between patients failing or passing were the SDSA Dot Cancellation and Road Sign Recognition subtests, AMIPB Design Learning and AMIBP IP Task (Learning Skills) "B" adjusted score. Eighty-five percent of those individuals who failed on the road and 90 % of those who passed were correctly classified.

Discussion

MS-related disabilities have great impact on employment, social functioning and driving performance. Sensory-motor symptoms and cognitive impairment may influence driving skills in patients suffering from RRMS.

Nearly half of all MS patients exhibit measurable neuropsychological deficits as compared to demographically matched healthy controls [1, 2]. Cognitive dysfunction is insufficiently described in many studies, as they often only use the EDSS.

The MSFC developed by the NMSS Task Force has better reliability and greater sensitivity to change as compared to the EDSS. It also includes information about cognition by using the PASAT [2].

Decisions concerning fitness to drive are often made on the basis of off-road evaluations, although driving is a multifaceted task which is also influenced by learned elements in the daily driving experience. On the other hand, in all studies concerning driving with MS, driving ability was not influenced by the duration of the disease or the length of time having had a driving licence. Investigators usually did not ask how long patients had a break from active driving.

Specially designed vehicles and assistance technology allow even patients with severe physical disabilities to drive a car. Neuropsychological assessment is a dominant factor for predicting driving fitness.

There is still no consensus on a suitable instrument for assessing driving abilities, especially by expert opinion [9, 24]. Driving is a task that requires divided attention as well as speed and lane control. Tests should be short to administer and easily interpreted by trained professionals. Driving simulators must include tracking and visual search [25].

Kotterba et al. [17] demonstrated cognitive impairment as assessed using the PASAT in RRMS patients. Though the patients also presented some deficits in arm function, only PASAT results correlated with driving disabilities. Results were reproduced in a second study with follow-up investigation over 24 months [21]. In the study by Schultheis et al. [5], patients with cognitive deficits demonstrated poorer performance in some subtests of the two computerized driving tests than did patients without cognitive deficits. Though the Neurocognitive Driving Test (NDT) included a steering-wheel and foot pedals, it is mainly a computer task assessing divided attention.

Regarding drugs such as antispasticity agents, tricyclic antidepressants, benzodiazepines, and anticonvulsant, they may cause sleepiness and fatigue and disable driving skills. On the other hand, patients may overcome their disease symptoms by using these medications and thus be enabled to drive [26]. MS-modifying therapies (mainly interferons and glatimere acetate) have a positive influence on the course of the disease (reduce disease progression, relapse rate, and especially cognitive deterioration in RRMS and secondary progressive MS, [27, 28]). They may have a positive influence on cognitive skills. Fischer et al. [27] demonstrated improvement in visual constructive abilities and memory skills and stabilised results in PASAT during two years of treatment with the disease-modifying drug intramuscular interferon beta-1a (IFNβ-1a).

Not only EDSS but also PASAT results were improved during therapy with intramuscular IFNß-1a [21, 23]. An improvement in driving was confirmed by a study during 24 months of therapy with interferon ß-1a [21]. Patients initially exhibited more mistakes in the driving simulator skill but ended up with scores equal to controls.

The studies demonstrate the need to also focus on driving skills even in MS patients with mild physically impairment. The risk of accidents in particular should be discussed following relapses. Great inter-individual differences occur, however, and there is a marked discrepancy between subjective and objective measures of cognitive function [29]. Especially when expert opinion is required, standardized investigations must be performed to assess physical and mental status. As the PASAT only assesses working memory and divided attention, broader neuropsychological testing should be added in this context. The driving simulator seems to be an additional, useful instrument for judging driving ability. As it is close to a real traffic situation, on-road evaluation may not be necessary in cases with ambiguous neuropsychological test results.

As driving ability has a great impact on social functioning and employment, MS patients wish to maintain their ability to drive. Therefore, stabilization of the course of the disease by immune-modulating therapy is necessary.

Conclusion

Driving function in multiple sclerosis is mainly influenced by cognitive deficits. Ability to drive must be assessed, even in mildly disabled patients and, in particular, following relapses. Computerized neuropsychological tests show the best predictive results when compared to on-road tests. Recommended drugs may influence attention. Disease modifying drugs, especially intramuscular interferon ß-1a, have a beneficial effect on neuropsychological deficits and driving skills.

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Drugs, Driving and Traffic Safety
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Drugs, driving and traffic safety in acute and chronic pain

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Abstract

Pain is a common reason for seeking health care and the economical burden of pain to society is high. Careful estimates state that 20% of the population has chronic pain, defined as pain which persists for a longer period, usually taken to be 3 or more months. Chronic pain severely disrupts various aspects of daily life. Unemployment, disability, and relational problems are frequently encountered among individuals with chronic pain. Chronic pain may have negative effects on driving ability. Effective treatment of pain is thus important, both in terms of improved quality of life of the patient and traffic safety. Several classes of pharmacological agents are being used to treat pain. Unfortunately with the currently available treatment options, pain is often not completely relieved. Furthermore, many of the pharmacological agents have side effects that may affect driving in its turn. This chapter provides an overview of the recent insights on the effects of pain and its treatment with pharmacological agents on driving ability and traffic safety.

Acute and chronic pain

Pain is an evolutionary important response and is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience, associated with tissue damage or described in terms of such damage” [1]. Pain serves to warn of potential or actual injury, and encourages inactivity to promote healing [2]. Patients seek health care for diagnostic reasons and for pain relief. Acute pain usually resides after healing of the injury, tends to respond to medical treatment, and is mostly regarded as a symptom. When pain persists for three months or more it is classified as chronic pain [1]. Chronic pain can be associated with progressive disease or can occur as an isolated manifestation without any ob-

vious medical cause. Chronic pain is a major public health care problem and is one of the most common reasons for seeking medical consultation [3].

A large epidemiological study demonstrated that in 15 centers located in different countries world-wide, nearly 20 % of primary care patients suffer from one or more chronic pain conditions, but prevalence rates varied (between 5 % and 33 %) between countries [4]. Patients with persistent pain are more likely to have anxiety or depression as comorbid diseases, experience more limitations in daily activity, and have unfavorable health perceptions [4]. Chronic pain is more prevalent in females [5, 6]. Pain significantly impacts employment status, causes emotional distress, and its effects on quality of life can be profound [7]. Economic costs associated with chronic pain are considerable [8].

Chronic pain is widely regarded as a condition which involves biological, psychological, and social factors that dynamically interact with one another (e.g., [9]). In the biopsychosocial model, which is used as a treatment approach, biological and psychosocial factors are taken into account. Depression, somatic awareness (hypervigilance to bodily sensations), pain-related fear (fearful evaluation of pain) and catastrophizing (having exaggerated negative orientation toward pain stimuli and pain experience) are acknowledged as playing a major role in the maintenance and etiology of pain-related problems [10, 11]. Increasing evidence suggests that catastrophizing and fear of movement may lead to avoidance behaviors and hypervigilance to bodily sensations, which in turn may lead to disability and depression. These factors have even been argued to play a role in the transition of acute to chronic pain. Pain is thus a multifaceted sense, the perception of which is subjective. Patients who suffer from long-lasting pain with a predominantly psychosocial component should be referred to specialized pain clinics for further diagnostic assessment and possible allocation to multidisciplinary pain management programs.

Traffic safety: methods to assess driving ability

Epidemiological studies are able to establish the relationship between medical conditions and/or drug use and traffic accidents. These studies, however, are usually not detailed enough to differentiate between specific medical conditions or specific drugs within a broader drug class, and often lack specific information on important issues such as time after drug intake, duration of drug use, and compliance to prescription instructions. Unfortunately, this method of retrospective evaluation of accidents that have already occurred is not able to predict risk of accident involvement in individual patients. Methods that have a predictive value are preferred. Laboratory tests, such as reaction time tests, psychomotor tests and attentional tasks, examine driving-related skills under controlled, standardized conditions. Although laboratory tests do not cover driving ability as a whole, they are useful in investigating specific skills and abilities that are involved in driving under controlled circumstances. The complex interaction of cognitive and psychomotor abilities is best studied in simulated or real driving circumstances. The driving test currently available which mimics real driving closest is the on-the-road driving test, which

has been applied in over 50 studies with both healthy volunteers and patients [12, 13]. The driving method has been calibrated by demonstrating its sensitivity to the effects of alcohol in a dose-related manner, with an increase in standard deviation of lateral position (SDLP) of approximately 2.4 cm at blood alcohol concentration (BAC) 0.05 % [14]. The SDLP is a measure of the amount of weaving of the car on the road, and the primary variable of interest in the on-the-road driving test.

Pain and traffic safety

Very few studies have examined the effects of poor health in relation to traffic accidents. Preliminary results show that poor health can predispose drivers to increased risk of involvement in crashes or injury during a crash with conditions such as stroke, heart disease and arthritis, especially in the elderly [15, 16, 17]. However, another epidemiological study did not find increased risks of vehicle crashes for drivers with a medical condition after adjusting variables such as age, mileages per years driven, driving habits, and sociodemographic characteristics between comparison groups [18]. The type of medical condition was not specified in this study. A recent epidemiological study on the effects of pain and pain treatment showed that pain alone or in combination with pain treatment was associated with increased traffic accident involvement [19]. Unfortunately, this study was unable to differentiate between pain and analgesic drug effects.

Several studies report on impaired cognitive function in chronic pain patients, particularly on attentional aspects [20, 21, 22, 23, 24]. Studies on experimentally induced pain in healthy controls yielded more conflicting results (e.g., [25, 26]). Several factors might account for different findings between pain patients and healthy controls. Pain catastrophizing, somatic awareness, and fear-related pain have been demonstrated to extend the attentional demand of pain [27]. These factors are likely to be present more in chronic pain patients compared to healthy controls, therefore attentional deficits may be more consistently found in chronic pain patients compared to healthy controls. Deficits in attentional functions in chronic pain patients may have a significant impact on driving performance.

No studies so far have assessed the effects of acute pain on actual driving performance, and only one study examined the effects of chronic pain on driving performance [28]. In this study, the on-the-road driving test was used. The observed difference in SDLP for chronic pain patients relative to age, education and driving-experience-matched healthy controls corresponded to that observed in healthy volunteers after consuming alcohol up to a blood alcohol concentration of 0.08 % [14], which is above the legal limit for driving a car in most (European) countries. Psychotropic drug use was not allowed in this study. A few patients used acetaminophen (paracetamol) and/or nonsteroidal anti-inflammatory drugs (NSAIDs) during the study. *Post hoc* analysis showed that SDLP differences between groups remained significant when these patients and their matched healthy controls were omitted from the analysis. The study thus demonstrates that chronic pain may significantly impair driving performance. These results need to be confirmed by other

studies, and future studies are needed to examine whether specific pain patients are at more risk. However, the clinical relevance of the observed impairment in driving performance in pain patients is evident. Importantly, the results of this study demonstrate why effective pain treatment is of major interest with respect to traffic safety, besides the potential of improving quality of life for the patient.

Mechanisms of pain

The underlying mechanisms of pain and its associated treatment are very complex, differ for pain conditions, and are still largely unrevealed. The treatment of pain by pharmacological drugs can be understood best by differentiating between inflammatory or "nociceptive" pain, which commonly results from continuing tissue disease or injury, *versus* neuropathic pain, which results from affected or injured neural tissue [29]. The distinction between inflammatory and neuropathic pain should not be viewed as a strict categorical distinction, since in many pain conditions they co-occur [29].

The mechanisms of inflammatory pain are reviewed by Kidd and Urban [30]. In short, tissue damage results in the release of inflammatory mediators from damaged cells and cells in the vicinity of the injury, including bradykinin, histamine, prostaglandins, cytokines, and substance P. These mediators all decrease the threshold of activation of nociceptors, which are specialized sensory receptors of primary afferent sensory neurons whose cell bodies are located in the dorsal root ganglia and trigeminal ganglia [31]. Nociceptors are activated by noxious stimulation of cutaneous and deep somatic tissues, such as muscles or joints, and respond to a variety of thermal, chemical and mechanical stimuli. The primary afferent sensory neurons synapse with second-order neurons in the dorsal horn of the spinal cord. Sensory information arising from noxious stimuli is then relayed to supraspinal subcortical structures including the thalamus and brainstem, and finally to the cortex. Acute pain is most often inflammatory. Once the tissue injury heals, the nociceptive action is terminated and the subject no longer experiences pain. In contrast, in chronic pain conditions, pain persists after the expected time frame for healing. In many cases, no underlying pathology can be found in chronic pain syndromes.

Neuropathic pain is initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system (or both), marked by positive and negative sensory symptoms and signs, such as spontaneous (stimulus-independent) pain, paresthesia (abnormal sensations such as burning or prickling), allodynia (pain in response to a normally non-noxious stimulus) and hyperalgesia (increased pain in response to a normally painful stimulus), and various degrees of sensory and motor deficits [29]. Underlying causes include infections, trauma, surgery, and inherited neurodegeneration. Demonstrating a lesion of the nervous system compatible with specific symptoms and signs provides strong support for considering pain to be neuropathic, although this is not always possible [32]. Chronic neuropathic pain is common in clinical practice, and includes conditions as diverse as diabetic neuropathy, postherpetic neuralgia, painful radiculopathy, HIV myelopathy, trigeminal

neuralgia, and phantom limb pain [29, 32]. It generally gives rise to a "burning", "shooting", or "electrical" sensation. Concerning the underlying mechanisms of neuropathic pain, it has been proposed that, in general, in response to injury or inflammation, nociceptors will turn to a state of hyperexcitability, which will trigger central neurons to undergo functional changes. Normally, these phenomena extinguish as the tissue heals; however, when the primary afferent neurons are altered in an enduring way, these processes persist, and may be highly resistant to treatment [32]. This mechanism is referred to as "sensitization".

Treatment of pain

Health care providers prescribe psychotropic medicinal drugs to patients with pain on a daily basis. However, advising patients regarding driving ability is difficult, since there is insufficient knowledge about the influence of pain and its treatment on driving performance. It should be kept in mind that pharmacological treatment of chronic pain is not a cure, only symptom management, and rather should be considered as an integral part of a more comprehensive treatment approach, including invasive procedures (e.g., nerve blocks), physical, and psychological treatment [32].

In acute pain cases, pharmacological treatment is often effective in relieving pain considerably or even completely. However, for chronic pain, drug treatment is often inadequate and other treatment options need to be considered as well. Pharmacological treatment of acute and chronic pain will depend on the specific diagnosis, individual characteristics, and type of pain. Acetaminophen and NSAIDs are among the most widely used drugs for the treatment of mild to moderate nociceptive acute or chronic pain. NSAIDs and acetaminophen are thought to act primarily peripherally; however central effects have also been observed [33]. These drugs have advantages over other drug classes as their side effects profile is generally low.

Opioids are used in the treatment of moderate to severe acute and chronic cancer pain. Increasingly, opioids are also prescribed in the treatment of chronic nonmalignant pain [34], but serious side effects such as constipation, nausea, itch, drowsiness, and sleepiness can occur [35, 36]. These side effects can sometimes be avoided by prescribing a lower dose of opioid with acetaminophen or NSAIDs. Alternatively, drugs with laxative and anti-emetic properties can be used. With prolonged opioid therapy, tolerance to side effects may occur. A drawback of prolonged therapy with opioids is decreased effectiveness or even opioid induced hyperalgesia and dependency [37]. Pain is sometimes undertreated because of fear of dependency. Some studies signal critical problems with long-term opioid therapy in efficient pain relief, improvement of quality of life, and functional capacity [38]. These studies point to the necessity of cautious approaches in treatment and careful examination of efficacy. The findings suggest that not all patients benefit from long-term opioid therapy. For patients who benefit from opioid use in terms of pain relief, it improves quality of life considerably.

Pharmacological treatment of neuropathic pain is more complicated. In general, patients do not respond to classical analgesics such as NSAIDs. The effectiveness of opioids in the treatment of neuropathic pain has been questioned, but recent studies suggest that it may be beneficial in higher doses [39]. In contrast, the efficacy of tricyclic antidepressants (TCAs), anticonvulsants (carbamazepine, gabapentin and pregabalin), and lidocaine have been consistently demonstrated [32]. Recommendations of first-line drugs are based on positive results from multiple randomized controlled trials. For several years now, TCAs have been considered first choice for most neuropathic pain disorders and are effective analgesics (both in terms of pain relief and occurrence of side effects) in approximately half of patients [40, 41]. TCAs have an analgesic effect that has been demonstrated to be independent of its antidepressant effect [32]. The exact mechanism of these agents as analgesic drugs is unknown. Several receptor actions and effects on ion channels potentially induce analgesia, including inhibition of norepinephrine and serotonin reuptake, affinity for μ-opioid receptors (although affinity is low), NMDA-antagonist-like effects, α_1-adrenergic receptor blockade, muscarinic cholinergic receptor blockade, antihistamine action, calcium channel blockade, and sodium channel blockade [42].

There are thus three broad classes of commonly used analgesic drugs: 1) nonopioid analgesics including acetaminophen and NSAIDs, 2) opioids, and 3) adjuvant drugs which have primary indications other than pain, such as antidepressants and anticonvulsants. Choice of analgesic drug treatment is based on pain diagnosis, severity of pain, and several individual characteristics. Since most pain patients are treated in an outpatient setting, they are likely to engage in normal daily activities, including driving. Side effects of analgesic drug use, such as sleepiness, drowsiness, and concentration loss, may negatively affect driving performance and increase the risk of becoming involved in traffic accidents. Based on previous findings, patients are often advised to be really careful or even to stop driving completely when taking psychotropic drugs. Most studies on effects of analgesic drugs on driving, however, are of limited value because they were carried out in healthy volunteers. The mechanisms of action and the profile of side effects can be very different when prescribed for the treatment of an underlying disease. To complicate matters, the underlying pain syndrome for which pharmacological drug treatment is required may also affect driving. The benefit of pain relief may temper the sedative side effects of analgesics or may even lead to improved performance. Hence, it is important to establish the effects of analgesic drugs in pain patients on driving ability in order to improve advice that should be given to patients on issues related to traffic safety when prescribing these analgesic drugs. Effects of drug use in relation to traffic safety will be discussed below for each broad class of analgesic drugs separately (see also [43]).

NSAIDs, acetaminophen and traffic safety

Epidemiological data show that, when using NSAIDs, the elderly are at risk of being at-fault in traffic accident involvement [44, 45]. Increased risk of traffic acci-

dent involvement in the elderly using NSAIDs might be explained by the impact of the clinical pain syndrome. However, independent contribution by NSAID use on increased crash risk in the elderly was also found. These effects could be explained by undiagnosed pain problems or the impact of NSAIDs on cognitive function [45]. No epidemiological studies have examined effects of acetaminophen or NSAIDs in adolescents, or middle-age adults. Although few studies have examined effects of NSAID on laboratory test performance, effects on cognitive function and psychomotor speed seem minimal [46]. Only one study examined effects of an NSAID on driving ability. This study did not find any effects on driving performance with use of the NSAID bromfenac in healthy adult subjects [47], but bromfenac was withdrawn from the market due to hepatotoxicity.

Opioids and traffic safety

There is much uncertainty about the effects of opioid use on the ability to drive a car. Epidemiological studies examining opioid use and its relation to traffic accident risks showed that opioid use, even in the elderly, did not increase the relative risk of becoming involved in a car traffic accident, in contrast to the benzodiazepine or tricyclic antidepressant drugs [48]. However, other studies showed increased accident risk for drivers using opioid drugs [49, 50]. Conflicting results of reports on healthy control subjects exist on the effects of opioids on cognitive and psychomotor functioning. Some studies report negative effects [51, 52], while others find no detrimental effects of opioids [53]. A study on the acute effects of the opioid oxycodone on driving performance in healthy, pain-free controls found no significant driving impairment. However, subjects reported that more effort was needed to drive safely and that they felt sedated [47]. These studies on cognitive function and driving performance have been performed in healthy subjects receiving drugs.

In order to evaluate effects of opioids on driving ability properly, it is important to consider the population tested, the drug, drug dosage, compliance with drug usage, and individual characteristics. Occurrence of negative side effects with opioid use may potentially affect the ability to drive. On the other hand, opioid use may also have beneficial effects due to pain relief. Indeed, analgesic morphine dosages have been demonstrated to improve cognitive performance as recorded by evoked potentials instead of deteriorating performance when given in the treatment of pain [54]. Thus, opioid sedation may be prevented by the presence of pain. In fact, it has been proposed that pain may impair performance more than opioid treatment [55]. Other studies reported on impaired neuropsychological functioning in chronic non-malignant pain patients receiving long-term opioid treatment, particularly on attention, psychomotor speed and working memory [56]. However, these studies were unable to distinguish between effects of pain and analgesic medication. Dellemijn et al. [57] showed that side effects of opioid use decline over time as tolerance to the adverse events develops, thus duration of therapy may be an important factor that should be taken into account as well.

Table 1 Effects of analgesic opioids on performance related to driving in chronic pain patients.

Reference	Drug regimen (mean dose)	Patients using opioids (N)	Control group(s) (N)	Tests	Performance
Vainio et al. [59]	stable morphine (209 mg oral daily)	cancer pain (24)	pain-free cancer patients (25)	test battery	overall not impaired except impaired balancing ability with closed eyes, improved performance on finger tapping
Galski et al. [60]	long-term opioid use (unspecified)	chronic non-cancer pain (16)	cerebrally comprised patients (327)	test battery & simulator	no significant impairment, on some tests better performance
Sabatowski et al. [61]	long-term transdermal fentanyl (30 µg/h)	chronic non-cancer pain (21)	healthy controls (90)	test battery	no significant impairment
Byas-Smith et al. [62]	stable opioid use (unspecified)	chronic pain (21)	healthy controls (50) pain, no opioids (11)	test battery & obstacle course & community drive	no significant impairment related to opioid use
Dagtekin et al. [63]	stable transdermal buprenorphine (45 µg/h)	chronic non-cancer pain (30)	healthy controls (90)	test battery	no significant impairment
Gaertner et al. [64]	opioid dose change (unspecified)	chronic non-cancer pain before and after dose change (32)		test battery	no significant impairment after 7 days of increase in dose

Abbreviations: N = number of patients included. In most studies, long-term or stable treatment corresponded to at least two weeks of stable doses.

Several studies examined driving ability in chronic pain patients receiving opioid therapy (reviewed in [58] and presented in Table 1). Vainio et al. [59] examined driving ability in cancer patients receiving long-term morphine for pain symptoms for at least two weeks, compared to the performance of pain-free cancer patients. Performance was tested on psychomotor tests originally designed for motor vehicle drivers. Patients using continuous morphine did not perform significantly worse on these tests. Driving was also unimpaired in a simulator evaluation study which examined chronic non-malignant pain patients on stable dose opioids [60]. Long-term treatment with transdermal fentanyl also did not affect performance related to driving as assessed in noncancer patients with a computerized test battery [61]. A recent study examined the effects of a wide variety of opioids used in the treatment of chronic pain on driving ability [62]. Patients were evaluated on driving their own car in the community and on an obstacle course. Patients who used opioids were compared to patients who used non-opioid drugs for pain relief and to healthy controls. None of the driving tests showed significant differences between groups. Another study also found no significant effects of long-term use of transdermal buprenorphine, a partial μ-opioid receptor agonist and a κ-opioid antagonist, on the German test battery assessing driving safety [63]. One study examined the effects of opioid drug dose changes on cognitive and psychomotor performances affecting driving ability. Seven days after opioid dose change, no deterioration was observed as compared to before opioid alteration on a series of tests examining driving safety based on international and national recommendations [64]. Unfortunately, no information is available on performance measures closer in time to the opioid dose changes. A structured, evidence-based review of the literature determined that there was no consistent evidence that opioid use is associated with motor vehicle accidents [65]. Based on these and others results and clinical impressions, the current opinion is that use of stable doses of opioids is unlikely to affect driving performance [59, 66]. Zacny [67] concluded that when opioids are taken for pain relief and/or with repeated stable doses, little effect of opioid use can be expected to be observed on skills related to driving. Recommendation of this author is to cautiously advise patients that stable use of an opioid for medical reasons is unlikely to affect driving performance [67]. Nevertheless, it should be noted that in several countries worldwide driving is still forbidden when using opioids.

These studies suggest that at least subsets of patients with chronic pain on stable opioid dosages are able to drive a car safely. These results contradict absolute prohibition of driving with opioids used for pain relief. More studies are urgently needed in this field to draw firm conclusions about the effects of specific opioids and dosages in patient populations.

Antidepressants and traffic safety

Although antidepressant drugs are not approved by the Food and Drug Administration for the treatment of chronic pain, they are frequently prescribed for neuropathic pain. They are generally more effective than classical analgesic drugs [41].

The analgesic effects of antidepressant drugs are thought to be dependent on both serotonergic and adrenergic actions. Tricyclic antidepressants (TCAs) inhibit both reuptake of serotonin and noradrenalin and are effective in relieving pain with a neuropathic component. The secondary amines, such as desipramine and nortriptyline, are considered to be effective as well, although evidence in randomized controlled trials is lacking. The newer selective serotonin reuptake inhibitors (SSRIs), the serotonin-noradrenergic reuptake inhibitors (SNRIs), and antidepressants with other mechanisms of action such as, e.g., inhibition of monoamine oxidase-A, seem to be less effective pain relievers. The analgesic actions of the tricyclic antidepressant drugs are independent of their antidepressive action. Of concern, drugs of the tricyclic class, such as imipramine and amitriptyline, have profound sedative effects, particularly as a result of the blockade of cholinergic, adrenergic, and histaminergic receptors.

Epidemiological studies showed that tricyclic antidepressant use can increase relative risk of car traffic accident involvement in the elderly [48, 49]. Other studies, however, found no association between traffic accident risk and use of antidepressant drugs [45, 68]. Several antidepressant agents have been tested in healthy control subjects for their effects on driving performance [69]. The newer antidepressant drugs, such as the SNRI venlafaxine [70] or the SSRIs fluoxetine and paroxetine, generally do not impair driving performance [71, 72]. However, the older tricyclic antidepressants do seem to impair driving performance and/or psychomotor performance in healthy control subjects, particularly after acute doses (e.g., [69, 70, 71, 73, 74]). It should be noted, however, that the doses of TCAs used in the treatment of pain are generally much lower than the antidepressant doses as tested in these studies. Furthermore, antidepressants prescribed for pain relief are usually taken nocturnally, which may decrease impairment of performance during the day. Relief of pain may also contribute.

One of the most effective and most frequently prescribed TCAs in the treatment of chronic neuropathic pain is amitriptyline. A recent study demonstrated that after a relative low acute dosage of 25 mg nocturnally administered amitriptyline, next day driving performance (approximately 13 hours after intake of the drug) was significantly impaired in chronic neuropathic pain patients compared to placebo [75]. The impairment in driving performance was comparable to a blood alcohol concentration of higher than 0.05%. After two weeks of treatment, performance deficits were no longer observed, which suggests that tolerance developed to the impairing side effects of amitriptyline. These results were based on a very small sample size, so further research is needed to ascertain these findings. No other studies have been performed in chronic pain patients to the effects of analgesic antidepressant use on driving performance.

Anticonvulsants and traffic safety

Few studies have examined the effects of anticonvulsant drugs on driving ability, as this medication is registered to be used for patients with epilepsy and these patients

are generally prohibited from driving because of risks of convulsions when driving. Increasing use of these drugs for other syndromes, such as chronic pain, indicate the need for studies on anticonvulsant drug use and traffic safety. The most commonly prescribed anticonvulsant drugs in the treatment of pain are carbamazepine, gabapentin, and pregabalin. Use of these anticonvulsant drugs often results in pain relief [32]. The mechanisms of action of anticonvulsants in relieving pain are still unclear. The latter agents bind to the α_2-δ subunit of calcium channels, thereby decreasing release of glutamate, norepinephrine and substance P [76], which may potentially induce analgesia. Side effects of anticonvulsant drug use are sleepiness and loss of concentration, amongst others.

Anticonvulsant drugs generally impair cognitive functioning, at least when tested upon initiation of therapy in healthy controls or patients with epilepsy [77]. A recent report indicated that the effects of drug use on driving may depend on the type of drug that is taken. The older drug carbamazepine impaired driving performance in healthy adults even after eight to twelve days after the start of drug intake, while the newer drug remacemide had no negative effects on driving performance [78]. No studies have been published on the effects of anticonvulsant drug use in chronic pain patients. A recently attempted study on the acute and subchronic effects of gabapentin on driving performance in chronic noncancer patients was terminated early because withdrawal effects developed from discontinuation of gabapentin in several patients in the initial washout period of the study (personal findings, unpublished), which appears not to be uncommon [79].

Warning labels on analgesic drug packages and traffic safety

The studies reviewed above demonstrate that some psychotropic drugs may affect driving performance and may increase the risk of road traffic accident involvement, even when prescribed for pain relief. Therefore, in several countries the packages of such psychotropic drugs have warning labels to provide information on possible driving impairment. The question remains as to whether warning labels influence the decision to drive while under the influence of medication with psychotropic side effects. This question was addressed in a recent study in pain patients, which demonstrated that warning labels have little impact on patients' decisions whether to drive a car or not. The majority of patients who used psychotropic medicinal drugs for pain relief reported driving a car regularly [80].

Conclusions

The ability to drive a car is important in maintaining independence in the community. Pain and analgesic drug use have been shown to be able to impair driving performance significantly. Unfortunately, no firm conclusions can be drawn based on the studies described in this chapter. More studies are needed on the possible

impairing effects of psychotropic medicinal drugs and the underlying diseases on driving and the risk this poses for traffic safety. However, several recommendations can be made. Importantly, it was demonstrated that chronic pain can affect driving performance. Therefore, the safety of drivers with chronic pain is of concern. Timely identification of pain and proper treatment may decrease effects on driving performance and increase traffic safety. However, sometimes pain control can only be achieved by pharmacological treatment, which is associated with the occurrence of central nervous system side effects. This is particularly the case in the treatment of chronic neuropathic pain with tricyclic antidepressants. Patients using these drugs should be advised not to drive during the initial phase of analgesic drug treatment, when dosage adjustments take place, or when patients restart their intake after a short medication break (e.g., after forgetting to take medicines). They should not drive if they do experience serious side effects, such as sedation. Patients should also be advised that their driving ability may be impaired in the absence of any subjective symptoms. Individual variability of test results warrants individual assessment.

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Drugs, Driving and Traffic Safety
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Drugs, driving and traffic safety in allergic rhinitis

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Abstract

Antihistamines are used as a treatment for allergies but cause sedation as a side effect. This sedation can be so severe that it interferes with patients daily functioning such as driving a vehicle. This chapter gives an overview of the effects of numerous antihistamines on driving performance as assessed in a standard highway driving test. When investigating the effects of an acute administration of the therapeutic dose, many antihistamines cause driving impairment comparable or larger than the effect of 0,5 mg/ml alcohol (i.e. hydroxizine, emedastine, diphenhydramine, clemastine, triprolidine, mizolastine, mequitazine, dexchlorpheniramine CR). However this does not mean that the other antihistamines are free of sedating effects. Driving impairment has been demonstrated for most antihistamines after increased or repeated doses. Also women often appeared to be more sensitive for the sedating effects of antihistamines. So far, only a few antihistamines appear to be free of impairing effects on driving (i.e. desloratadine, levocetirizine, fexofenadine and rupatadine), however, not all have them have been tested after higher or repeated dosing. This review of more than 15 driving studies indicates that most antihistamines have the potential to impair performance. Therefore patients should be correctly advised and informed about the possible risks when choosing a treatment.

Introduction

As many as 20% to 30% of the population are estimated to suffer from allergic conditions such as allergic rhinitis, hay fever or urticaria [1, 2]. Antihistamines, or H1-antagonists, are used as an effective treatment and act fast to relieve symptoms in a majority of patients. The most frequently reported side effects include gastro-intestinal complaints, dry mouth and, most importantly, drowsiness. This drowsiness can be so serious that it affects daily patient activities such as studying, working, or driving an automobile. So, although symptomatic relief is provided,

the inconvenience of adverse effects may be more troubling than suffering from the untreated condition.

Antihistamines' main target for achieving their therapeutic effect is the peripheral H1 histamine receptor. Most antihistamines are selective for the H1-receptors and have little effect on the H2 or H3 histamine receptors. Besides H1-receptor blockade, several antihistamines produce weak to pronounced blockade of cholinergic, serotonergic, and adrenergic neurotransmission [3, 4].

The group of antihistamines includes chemically different compounds which all share the pharmacological capacity to prevent histamine from binding to its receptor and, consequently, diminish the symptoms of allergies. Most antihistamines are rapidly absorbed after oral administration and generally provide symptomatic relief within one or two hours. The elimination half-life of antihistamines varies considerably, ranging from a couple of hours to a few days [5–8].

It has been repeatedly demonstrated that there is a clear relationship between antihistamines and sedation or drowsiness. However, large differences exist between individual antihistamines, some causing excessive sedation, some causing no sedation at all, and some even producing activation. Often a distinction is made between first and second generation antihistamines.

First generation antihistamines readily cross the blood brain barrier and bind to H1-receptors in the CNS [9, 10], causing somnolence. Various studies have demonstrated a correlation between the amount of H1-occupancy and the sedative properties of antihistamines [11–13]. Other research has established that the use of first generation antihistamines is related to a decrease in work productivity [14], increased absenteeism from work or school [15, 16], and an elevated risk of traffic accidents [17–19] and occupational injuries [20].

In the 1980s antihistamines were developed that claimed to be less sedating. The reduced ability to cross the blood brain barrier was suggested as the reason for this decreased sedation [13, 21]. These second generation antihistamines are often called "non-sedating" antihistamines. Although they are less sedating than first generation antihistamines, patients occasionally report sedative side effects when treated with second generation antihistamines, especially when the therapeutic dose is exceeded [22, 23].

Recently, new antihistamines have been developed from existing compounds. These new antihistamines – fexofenadine, levocetirizine and desloratadine – are the active metabolites of terfenadine, cetirizine, and loratadine and were found to be as efficacious as their predecessors.

Over the years many studies have been published on the sedating effects of antihistamines. Different measures have been used to study the effects on attention, psychomotor performance, and other cognitive functions. This diversity of methods makes it difficult to objectively compare the sedating potential of different drugs. The standard highway driving test (SHDT), however, has been used to study the effect of almost every antihistamine on the market. This method has been proven reliable and has been consistent over the more than 25 years that it has been used. Therefore, this review will concentrate on the effect of antihistamines on driving performance using the standard driving test.

Acute effects

Most studies have investigated impairing effects after a single administration of a drug. This is indeed very relevant in the case of antihistamines, since most patients use their medication on an irregular basis, i.e. when they experience symptoms. The majority of studies have also tested at a time when the concentration of the drug was maximal in the blood.

The acute effects of *emedastine* (2 and 4 mg twice a day) were tested in only one driving study [24]. This study, in a mixed gender population, showed significant driving impairment three hours after drug intake. Emedastine increased standard deviation of lateral position (SDLP) by 4.2 and 4.6 cm at the 2 and 4 mg dosage, respectively.

Hydroxizine was recently used as an active control in a mixed gender driving study [25]. The 50 mg dose resulted in a significant SDLP increase of about 4.5 cm two hours after drug intake.

Once a day treatment with *diphenhydramine* 50 mg was used as an active control in three studies [26–28]. In the first study, which was performed on female subjects, diphenhydramine increased SDLP by 4.5 cm 1.5 hours after drug intake [26]. A repetition of the driving test 3.25 hours after drug intake resulted in an SDLP increase of 4.4 cm. The driving study by Verster et al. (2003), including equal numbers of male and female subjects and testing at 1.5 hours after drug intake, demonstrated a lower SDLP increase of 2.8 cm [28]. The third study tested diphenhydramine in a mixed gender population and demonstrated an SDLP increase of 3.9 cm two hours after drug intake [27]. In all three studies the SDLP increase caused by diphenhydramine was significantly different from placebo.

Clemastine 2 mg was studied as a once a day [29] as well as a twice a day dose [30]. The one-time administration resulted in the highest increase in SDLP (about 4.0 cm) 3.45 hours after drug intake, whereas the twice a day regimen showed a smaller but still significant SDLP increase (1.9 cm) three hours after drug intake.

Triprolidine has been used in several studies as the active control and has been administered in doses of 5 or 10 mg (controlled release formulation), in a once or twice a day regimen [31–35]. The highest significant SDLP increase (3.7 cm) was demonstrated in the 5 mg triprolidine twice a day regimen, between two and three hours after drug intake [33]. For the 10 mg controlled release formulation, the largest significant SDLP increase (2.9 cm) was demonstrated in a male population between two and three hours post-dose [32].

In 1994 *mizolastine* was tested in four different doses (5, 10, 20, and 40 mg) [29]. The two lowest doses had moderate, non-significant effects on SDLP, whereas the 20 mg and 40 mg doses significantly increased SDLP (2.3 and 3.3 cm, respectively). This study also demonstrated that females reached the sedative threshold after lower doses of mizolastine as compared to males.

Acrivastine was tested in a male- [32] and a female-subjects study [26]. In the first study acrivastine 8 mg three times a day did not lead to significant increases in SDLP. In female subjects, significant SDLP increments were demonstrated; acrivastine 16 mg increased SDLP about 2.5 cm (between 1.5 and 2.75 hours after drug

intake), whereas the 24 mg dose led to an increase of 2.8 cm (between 3.25 and 4.5 hours). The SDLP increase was not significant after 8 mg acrivastine, although it increased by almost 2.2 cm.

Dexchlorpheniramine 6 mg was studied as a controlled release formulation in two studies [36, 37]. Both studies were carried out in a mixed gender population and tested driving performance between three and four hours after drug intake. Dexchlorpheniramine significantly increased SDLP by 2.4 cm in the first study, and by 2.0 cm in the second.

Although *mequitazine* has been available for some time, it has only recently been studied using the highway driving test [36, 37]. The first study tested mequitazine in doses of 5, 10 and 15 mg once a day. Mequitazine increased SDLP in a dose-related manner. However, the separate doses did not reach significance. The 10 and 15 mg doses caused an SDLP increase of 1.0 and 1.1 cm, respectively [36]. In the second study the SDLP was significantly increased (2.5 cm) after mequitazine 10 mg treatment [37]. Although these results seem conflicting, it shows that some individuals are prone to the sedating effects of this antihistamine by demonstrating impaired driving.

Opinions on the sedating potential of *cetirizine* have differed ever since two contradicting studies appeared in 1992 [31, 38]. The different outcome is thought to be caused by two factors: time of dosing and gender of the population. The study by Ramaekers et al. (1992) found a significant SDLP increase of 1.9 cm in a mixed gender group [38]. A more recent study by Vermeeren et al. (2002) found a significant increase in SDLP only for female subjects in the study (approx. 2.5 cm) [24]. Both studies examined driving performance three hours after treatment.

Four studies have investigated the effects of *loratadine* on SDLP [33, 35, 38]. The highway driving test was performed between two and five hours after single 10 and 20 mg doses. None of these studies demonstrated a significant effect of loratadine on the driving test, although the effect approached significance (1.3 cm) two hours after dosing the 20 mg dose [33].

Over the years, several studies have tested the effect of *terfenadine*, in doses of 60, 120, and 180 mg, on the highway driving test [26, 31, 33, 35]. Terfenadine never demonstrated significant impairments on the driving test, not even in female population studies. The highest SDLP increase (1.2 cm) was found in a mixed gender population four to five hours after drug intake [33]. In several countries terfenadine is no longer available, due to its cardiotoxic effects [39].

The effects of *ebastine* were investigated in the standard driving test more than 15 years ago. The results were published as a technical report [34] and later reanalyzed by O'Hanlon and Ramaekers (1995). Instead of causing impairment, all doses tested (10, 20 and 30 mg) showed a decrease in SDLP, with 20 mg causing the highest decrease (– 1.2 cm) (data from two sessions combined: 2–3 h and 6–7 h).

Desloratadine, the active metabolite of loratadine, is a relatively new antihistamine. Driving performance was tested in one study using the therapeutic dose of 5 mg [27]. Desloratadine did not increase SDLP, but rather decreased it slightly (non-significant). Together with an improved reaction time in a car-following test, this suggests that desloratadine might have stimulant effects. Higher doses of desloratadine have not yet been tested using the standard highway driving test.

Levocetirizine, a relatively new antihistamine, is the active compound of cetirizine. A mixed gender study showed that levocetirizine 5 mg had no effect on SDLP when tested between 1.5 and 2.5 hours after intake [28]. Up to now, this is the only study on the effect of levocetirizine in the highway driving test and therefore the effects of higher doses of levocetirizine are unknown.

Fexofenadine is a relatively new antihistamine that was developed from terfenadine. One mixed gender study tested fexofenadine 120 and 240 mg as a single- and divided-dose regimen in the standard driving test [30]. The SDLP scores were not significantly higher than placebo. Instead, the results suggested stimulating effects of fexofenadine, as the 120 mg twice a day regimen caused an SDLP decrease (non-significant, about 0.9 cm).

Rupatadine, also a rather new antihistamine, was recently tested in its therapeutic dose of 10 mg [25]. When performing the driving test two hours after drug intake, the SDLP score was comparable to that of placebo treatment. Higher doses of rupatadine have, up to now, not been studied using the standard driving test.

These studies indicate that there is great variation in the impairment potential of antihistamines, with some posing serious risks to traffic safety. When administered in therapeutic doses, diphenhydramine, emedastine, and hydroxizine have been shown to cause driving impairment comparable to or greater than the effects of 0.8 mg/ml alcohol. Clemastine, triprolidine, mizolastine, acrivastine, dexchlorpheniramine CR and mequitazine impaired driving performance to the same extent as alcohol 0.5 mg/ml. Although the effect of the therapeutic dose of acrivastine was not significantly different from placebo, it did increase SDLP by 2.2 cm, demonstrating the clinical significance of the effect. For mizolastine a clinical and statistical effect was only demonstrated after higher than therapeutic doses. Studies on cetirizine demonstrated that it has the potential to impair driving performance, especially in sensitive subjects.

So far, only terfenadine, loratadine, levocetirizine, desloratadine, ebastine, fexofenadine and rupatadine have shown no impairment on driving in the standard driving test after acute administration. Their effects on SDLP were equal to placebo and, in some cases, even seemed to have improved it. One has to take into account, however, that levocetirizine, desloratadine, and rupatadine have only been tested in their therapeutic doses and not in higher doses.

Subchronic effects

Although most studies have concentrated on the acute effects of antihistamines on driving performance, several have also investigated the effect of repeated administration of the drug. Whether subjects develop tolerance or whether the drug accumulates in the brain can be demonstrated by studying subchronic effects.

Vermeeren et al. (2002) found that the effects of subchronic treatment with *emedastine* (2 or 4 mg bid) were only marginally less than the acute effects [24]. After four days of treatment, emedastine still significantly increased the SDLP by 3.0 and 3.85 cm, respectively.

Diphenhydramine, which showed serious acute impairment of driving, demonstrated a tolerance effect when given over four days [28]. In this study, diphenhydramine increased SDLP by 1.6 cm when tested 1.5 hour after drug intake (50 mg o.d.) on day four. Although this subchronic effect was smaller than the acute effect, it was still significantly different from placebo.

The subchronic effect of *clemastine* 2 mg (bid) was studied after four days of treatment. The SDLP increase was still approximately 1.5 cm greater than placebo, which was a significant effect compared to placebo [30].

The effect of *triprolidine* 5 mg (bid) was tested after four days of treatment in a mixed gender population. When testing two and four hours after drug intake, the SDLP was significantly increased compared to placebo (2.5 cm and 2.0 cm, respectively) [33]. In a male population, the SDLP after four days of treatment with triprolidine (5 mg bid) was also significantly increased (about 1.0 cm) compared to placebo, when tested one hour after the last dose [31]. The effect of a controlled release formulation of triprolidine (10 mg o.d.) was not significantly different from placebo after four days of treatment [32].

The subchronic effect of *dexchlorpheniramine* (controlled release formulation, 6 mg o.d.) was tested after eight days of treatment [37]. The results of this study demonstrated that dexchlorpheniramine no longer differentiated from placebo after prolonged administration.

The subchronic effect of *mequitazine* 10 mg o.d. was tested after eight days of treatment [37]. This study showed that the effect of mequitazine was no longer significantly different from placebo, although it increased SDLP by 1.1 cm.

Three studies investigated the subchronic effects of *cetirizine*. Vermeeren et al. [24] found that the SDLP increase in female subjects caused by an acute dose of cetirizine (10 mg o.d.) did not diminish after four days of treatment (1.8 cm). For the whole group, however, the SDLP increase (1.3 cm) was not significantly different from placebo on day four. The study by Volkerts et al. [31] in male subjects, and the study by Theunissen et al. [37] in a mixed population found no subchronic effect of cetirizine after four and eight days of treatment, respectively.

When tested after four days of treatment with *loratadine* 20 mg once a day, subjects showed a nearly significant increased weaving four hours after administration (1.3 cm) [33]. When these researchers tested the overall effect of loratadine on days one and four, the impairing effect reached significance. A 10 mg dose (o.d.) for four days did not increase SDLP in a male population [35].

One study tested the subchronic effect of *terfenadine* 120 mg (bid) at two different time periods after last intake on day four [33]. This study demonstrated a significant rise in SDLP when driving was performed two hours after intake (i.e. 1.7 cm), while, four hours after intake, the SDLP increase after terfenadine was no longer significantly different from placebo (1.1 cm). Two studies testing a male population between one and two hours after the last dose on day four showed no increase in SDLP after a 120 mg dose (unitary and divided dose) [31, 35].

Although the acute effects of *ebastine* suggested a stimulating effect on driving performance, impairment was demonstrated upon testing after five days of treatment. Ebastine 30 mg significantly increased SDLP by approx. 1.7 cm [40].

The effect of *levocetirizine* after four days was comparable to the acute effect and not significantly different from placebo [41].

Acutely, *fexofenadine* demonstrated mild but non-significant stimulating effects. When a 120 mg dose was administered twice a day over four days, the SDLP significantly decreased by 1.4 cm [30].

Table 1 Overview of studies demonstrating a significant increase in SDLP. The acute and subchronic effects are indicated in terms of blood alcohol concentration (BAC) required to achieve the same level of impairment. Abbreviations: BAC – Blood alcohol concentration; ns – not significant.

				BAC equivalent		
Antihistamine	**Dose**	**Time of testing (h) relative to dosing**	**Gender**	**Acute effect**	**Subchronic effect**	**Ref.**
Emedastine	2.4 mg bid	3	mixed	>0,8	>0,5	[24]
Hydroxizine	50 mg o.d.	2	mixed	>0,8	not tested	[25]
Diphenhydramine	50 mg o.d.	1.5 and 3.25	women	>0,8		[26]
	50 mg o.d.	2	mixed	>0,5	<0.5	[27]
	50 mg o.d.	1.5	mixed	>0,5		[28]
Clemastine	2 mg o.d.	3.45	mixed	>0,8		[29]
	2 mg bid	3	mixed	<0,5	<0.5	[30]
Triprolidine	5 mg bid	2	mixed	>0,5	>0.5	[33]
	5 mg bid	4	mixed	<0,5	<0.5	[33]
	5 mg bid	1	males	>0,5	<0.5	[31]
Mizolastine	20 mg o.d.	3.45	mixed	>0,5	not tested	[29]
	40 mg o.d.	3.45	mixed	>0,5		[29]
Acrivastine	16 mg o.d.	1.5	female	>0,5	not tested	[26]
	24 mg o.d.	3.25	female	>0,5		[26]
Dexchlorpheniramine CR	6 mg o.d.	3	mixed	>0,5	ns	[36]
Mequitazine	10 mg o.d.	3	mixed	>0,5	ns	[37]
Cetirizine	10 mg o.d.	3	females	>0,5	<0.5	[24]
	10 mg o.d.	3	mixed	<0,5		[38]
Loratadine	20 mg o.d.	2 and 4	mixed	<0,5*	<0,5*	[33]
Terfenadine	120 mg bid	2	mixed	ns	<0,5	[33]
Ebastine	30 mg o.d.	2 and 6 combined	males	ns	<0,5	[40]

*the effect of loratadine approached significance on days one and four, and was significant when tested overall.

In most cases the effects of antihistamines on driving performance diminished but were still significant when drug administration was continued over several days. The subchronic effect of emedastine and triprolidine was still equal to or greater than the effect of alcohol 0.5 mg/ml. A clear tolerance effect was demonstrated for dexchlorpheniramine and mequitazine. Only the effect of ebastine changed from acutely stimulating to subchronically sedating, probably as a consequence of accumulation in the brain.

Antihistamines in combination with alcohol

Of course, patients should be extra careful when combining drugs with alcohol; therefore, several studies investigated the combined administration of antihistamines and alcohol. For cetirizine, it was demonstrated that the effect of alcohol was additive to the effect on SDLP [38]. On the other hand, neither loratadine nor terfenadine in combination with alcohol had a greater effect on SDLP than alcohol alone [35]. And although many driving tests had to be stopped for safety reasons after the combined administration of emedastine and alcohol, emedastine did not add to the effect of alcohol [24]. Fexofenadine, on the other hand, was found to antagonize the effect of alcohol in a dose-related manner [30].

Antihistamines' effects on females

For several antihistamines, driving impairment was only demonstrated in an exclusively female population. A few studies also demonstrated women's greater sensitivity to the impairing effects of antihistamines, i.e. clemastine, mizolastine [29], acrivastine [26], emedastine and cetirizine [24]. These findings suggest that women might be more sensitive to the effects of antihistamines. It has been hypothesized that this greater sensitivity by women is a consequence of lower bodyweight; however, this has never been demonstrated.

Discussion

The standard driving test has proven to be an excellent tool to compare the sedating effects of antihistamines. Thanks to the calibration study by Louwerens et al. (1987) [42] it is possible to compare the effects of each antihistamine with a blood alcohol concentration (BAC) required to achieve the same level of impairment. One has to conclude that antihistamines that caused an acute SDLP increase of more than 2.2 cm (=BAC 0.5 mg/ml), such as hydroxizine, emedastine, clemastine, triprolidine and diphenhydramine, are to be avoided when possible. For antihistamines that reached an SDLP increase of more than 2.2 cm after repeated or

higher doses, caution is also in place. Only terfenadine, fexofenadine, levocetrizine, ebastine, desloratadine and rupatadine have, up to now, demonstrated to be free of driving impairment in acute dosing studies [25, 27, 28, 30, 40]. For fexofenadine, this was true even after higher and repeated doses, while levocetirizine also demonstrated to be safe in a repeated dose study. Ebastine, on the other hand, impaired driving performance when tested after high and repeated doses, while terfenadine impaired driving in a repeated dose study. The effects of higher or repeated doses of rupatadine and desloratadine have not yet been investigated using the standard highway driving test.

It appears that the antihistamines causing driving impairment comparable to or greater than the effect of 0,5 mg/ml alcohol after acute administration of therapeutic doses all belong to the so-called first generation antihistamines. Second generation antihistamine effects are lower than the effect of 0.5 mg/ml alcohol, but they are not free of sedating effects. Driving impairment has been demonstrated in higher doses, after repeated administration and/or in female subjects. Consequently, the term "non-sedating antihistamine", which is often used as a synonym for the second generation, is clearly not justified.

Because loratadine, fexofenadine, desloratadine, rupatadine and levocetirizine are relatively free of sedative effects, they might be preferred by patients over other antihistamines. These antihistamines are not yet classified as a distinctive group, but some researchers have suggested grouping them in a new category: the third generation antihistamines.

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Drugs, Driving and Traffic Safety
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Drugs, driving and traffic safety in diabetes mellitus

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Abstract

Several diabetes-related conditions can impair the driving ability of diabetic patients. These include visual loss due to retinopathy, sensory-motor impairment due to neuropathy, cardiovascular disease, and amputation. Caused sometimes by rapid onset, hypoglycaemic events belong to the most dangerous situations in traffic not only for the diabetic patient, but for other traffic participants as well. The main reason for hypoglycaemias is insulin therapy, but some oral antidiabetic drugs (sulfonylureas, glinides) in widespread use also have hypoglycaemia-inducing properties. To date, insulin therapy and its consequences on traffic safety have been at the focus of research.

Unfortunately, the available studies provide no consistent picture of the traffic safety of insulin-treated patients. Frequent methodological problems include retrospective analysis, not distinguishing between insulin-dependent and insulin-independent patients, no distinction between the different modes of insulin therapy, no clear emphasis and description of comorbidities and other medications of the patients. Furthermore, many of these studies rely on official data that only quantify accidents or traffic violations or are predicated on self reports. Although there is no doubt that hypoglycaemias during driving occur, the studies show a tendency – but no clear evidence – that patients with diabetes are significantly more involved in road traffic accidents than the population in general. The ambiguous picture presented by the different studies has led to variable strategies by the licensing authorities concerning diabetic patients throughout the world. Since the outcome of a traffic hypoglycaemia also depends on the patient's ability to detect and to counteract this situation, the increase in patient education of recent decades may have played a positive role. Apart from the participation of subjects with hypoglycaemia unawareness in hypoglycaemia awareness trainings, further recommendations include measuring blood glucose levels before and also during longer drives, especially for those individuals who have lost the symptoms of low blood glucose and have a history of driving mishaps.

Introduction

There are several reasons that can adversely influence traffic safety in patients with diabetes mellitus, including neuropathy, retinopathy or hypertension treated with drugs, and the cardiovascular complications of the disease in general. The focus of this article is on the effect of antidiabetic medication with possible hypoglycaemia-inducing properties, such as with sulfonylureas, glinides, and insulins. Hypoglycaemic events while driving cars belong to the most dangerous situations for a diabetic patient as well as for the community and is suggested to be the most frequent cause of accidents [1].

The belief that insulin-treated patients are at a higher risk of causing traffic accidents stems from the disabling effects of hypoglycaemia. The following chapter provides an overview of present knowledge concerning impaired traffic performance in a hypoglycaemic state.

Traffic performance in hypoglycaemia

Several studies have clearly demonstrated that cognitive and motor functions critical for driving (e.g. reaction time, hand-eye coordination, visual information processing, etc.) are impaired in a hypoglycaemic state [2]. It was the group of D. J. Cox that extensively studied the driving performance of diabetic patients by using driving simulators [3]. For example, in a study of 25 patients with insulin-dependent diabetes (no hypoglycaemia unawareness and no complications of the disease), driving performance was not affected by mild hypoglycaemia (blood glucose range 3.6 mmol/l or 65 mg/dl), whereas blood glucose levels averaging 2.6 mmol/l (45 mg/dl) did cause steering problems, swerving, spinning, crossing lanes, etc. This study used a simple single-screen driving simulator and tested five minutes of driving performance during stepped hypoglycaemia. Since the authors themselves addressed some limitations of the study (hypoglycaemia is a progressive and not a stepped process, hypoglycaemia would likely occur whilst driving and not at the time of driving initiation), they used a more subtle approach in following investigations using an Atari research Driving Simulator (detailed description, see [4]) providing a 160° visual field, a programmed rear view and a more realistic driving environment [4].

During this testing of 37 type 1 diabetic patients, driving performance, EEG, and corrective behaviours were continually monitored. Furthermore, blood glucose, symptom perception, and judgement concerning impairment were assessed every five minutes in three hypoglycaemic ranges (4.0–3.4, 3.3–2.8, and <2.8 mmol/l). The authors demonstrated the driving performance in all these hypoglycaemic ranges to be significantly impaired. In the patient group, corrective actions did not occur until blood glucose was <2.8 mmol/l (50 mg/dl).

In addition to this issue of concern, progressive hypoglycaemia not only impairs motor and neurophysiologic functions, but may also reduce symptom recognition and, therefore, the perception of driving ability at least in some subjects [5].

In the study of Weinger et al. [5], during a stepped hypoglycaemic insulin clamp in 60 patients with type 1 diabetes, serum glucose levels were reduced from 120 mg/dl to 80, 70, 60, 50, and then 40 mg/dl during 190 minutes. At each glucose level, patients completed a symptom questionnaire and neuropsychological test, estimated their glucose level, and reported whether they could drive safely. Among the results: men and middle-aged patients were more likely to consider it safe to drive during hypoglycaemia than women and those under 25 years of age. Patients who were symptomatic and those who recognized hypoglycaemia were less likely to report safe driving ability during hypoglycaemia.

However, given adequate hypoglycaemia awareness and the ability to handle such situations, hypoglycaemic events do not automatically have to end in traffic accidents.

There has been a raising awareness in recent years concerning the necessity of patient counselling, and a raising of their alertness as to how to detect hypoglycaemias and how to counteract them. With this in mind, there is apparently a tendency towards reporting a higher risk and incidence of unfavourable traffic events as the age of the literature increases.

Studies on traffic incidents and diabetes

One of the first studies to address the issue [6] was a retrospective analysis by Waller et al. from 1965. Based on data reported to the California Department of Motor Vehicles on traffic accidents and traffic violations, a sample of 2672 patients with chronic medical conditions was investigated for three years. As a subgroup, these data were analysed in 214 male and 73 female patients with diabetes mellitus, mean age about 40 years, in comparison to 922 healthy control persons. In this report, traffic violation rates were significantly higher (39%) in the diabetic group ($4.6/10^5$ miles *vs*. $3.3/10^5$ miles), as were accident rates ($15.5/10^6$ miles *vs*. $8.7/10^6$) (78%). Unfortunately, from the data report it is not possible to provide precise information on the mode of treatment of the diabetic patients or possible sequelae (visual impairment etc.) of the disease.

Derived from data from Washington's Department of Motor Vehicles data processing Center, Crancer and McMurray [7] compared driving records of 39 242 medically restricted drivers with driving records of all Washington motorists (1.6 million) from 1961–1967. In a large sample of 7646 patients with diabetes mellitus, statistically higher accident rates than the overall population of Washington drivers were reported. The average rate per 100 drivers in the time span of six years was 31.45 for accidents and 73.33 for traffic violations. For all Washington motorists, the average rate per 100 drivers in the time span of six years was 27.61 for accidents and 81.01 for traffic violations, respectively.

Another early study from Sweden [8] investigated 243 drivers with diabetes, 218 of them treated with insulin. Apart from the precise data on treatment mode, the degree of retinopathy of the patients was also described as a clear advantage of this study. Furthermore, there was an assessment of the number of kilometres driven per

year and the driving conditions (urban/rural, day/night). Diabetic drivers underwent an average observational period of 4.7 years and, based on data from the Driving License Registry in Göteborg, in comparison to a control group with a comparable number of km driven annually under the same driving conditions, only 1.7% of the insulin-treated patients were involved in road accidents. The frequency of road accidents and serious driving offences is even lower than in the healthy control group.

Unfortunately, many of these earlier studies fail to provide a consistent picture concerning the traffic safety of patients with diabetes. Frequent methodological problems include retrospective analysis, not distinguishing between insulin-dependent and insulin-independent patients, no clear emphasis and description of comorbidities and other medications of the patients. Furthermore, these studies frequently rely on official (governmental or health insurances) data that only quantify accidents or traffic violations. It seems reasonable to assume that these "end points" are not appropriate to reflect the traffic risk, and especially not the number of hypoglycaemic events a person with diabetes mellitus might experience during a driving career. The "outcome" of a symptomatic hypoglycaemia depends on factors such as the degree of traffic, the vigilance of other road users, the rapidity with which a hypoglycaemic event occurs, as well as also the adequate reaction of the affected person.

In a survey of 250 patients by Frier et al. from 1980 [9], the issue of traffic hypoglycaemias was more clearly addressed: eighty-six patients (34.4%) with insulin-dependent diabetes mellitus had had one severe or several frequent hypoglycaemic situations in the preceding six months, during which they had been driving regularly. Thirty-four patients (13.6%) had admitted involvement in a driving accident since the onset of treatment with insulin, and 13 of these patients furthermore reported that hypoglycaemia had been an important causal factor.

Recently, a brilliant systematic review of many of those studies with the primary objective of determining whether drivers with diabetes mellitus are at greater risk of a motor vehicle crash than comparable drivers without the disease was presented at the 4th International Driving Symposium on Human Factors in Driver Assessment, Training, and Vehicle Design, Skamania Lodge Stevenson, Washington, USA, July 9–12, 2007 by Tregear et al. [10]. The authors identified 16 articles addressing this question. Although an assessment of these studies based on evidence-based criteria and meta-analysis found most of the studies in a low-to-moderate range, a random-effects meta-analysis revealed that individuals with diabetes have a 19% increased risk of a motor-vehicle crash when compared to individuals without diabetes. Furthermore, the authors found no compelling evidence suggesting diabetic patients treated with insulin are at a higher risk of a motor vehicle crash than diabetic patients not treated with insulin. The following table and overview of the relevant studies is in part adapted from this work.

A Danish three-year follow-up study of 7599 persons with diabetes from 1997 based on insurance reports showed the risk of accidents in patients with diabetes even significantly lower than in control groups [19]. The risk of accidents was 0.7 per 1000 person-years in the diabetic group, compared with 4.5 per 1000 person-years. Seven-thousand and eighty-one of the patients with diabetes were under

Table 1 Case-control studies on the incidence of traffic accidents in diabetic patients. Primary outcome: differences in crash rate. Abbreviation OAD: oral antidiabetic drugs.

Reference (Year)	Patients with diabetes *vs*. Controls	Anti-diabetic therapy	Comorbidities reported	Report of outcome	Higher accident rate in diabetic patients
Waller 1965 (6)	287 *vs*. 922	Not specified	Not specified	Records California Dpt. of Motor Vehicles	yes
Ysander1966 (8)	256 *vs*. 256	Insulin, OAD	Retinopathy	Driving License Registry, Göteborg	no
Crancer and Mc Murray 1968 (7)	7646 *vs*. 1.6 Millions	Not specified	Not specified	Records State of Washington	yes
Davis et al. 1973 (11)	108 *vs*. 1650245	Not specified	Not specified	Records of Oklahoma Medical Advisory Committee	slightly higher in male, lower in female drivers
De Klerk and Armstrong 1983 (12)	8623 *vs*. expected rate	Not specified	Not specified	Hospital Admission Record Western Australia	yes in men < 55 yrs, not in the whole group
Songer et al. 1988 (13)	127 *vs*. 127 (sibling)	Insulin	Retinopathy, amputation	Self report	not in the whole group, higher in females
Eadington and Frier 1989 (14)	187 *vs*. "general population"	Insulin	Retinopathy, neuropathy	Self report	no
Stevens et al. 1989 (15)	354 *vs*. 302	Insulin	Heart disease, Retinopathy	Self report	no
Hansotia and Broste 1991 (16)	484 *vs*. 30420	Insulin, OAD	Cardiovascular disease, Neuropathy, Retinopathy, Amputation	Hospital records, Wisconsin	yes (slightly)
Laberge-Nadeau et al. 2000 (17)	4495 *vs*. 8958	Insulin, OAD	Visual, cardiovascular	Public insurer for automobile injuries and public health insurer Quebec	no in whole group, yes in diabetics not using insulin
Cox et al. 2003 (18)	341 (Type 1), 332 (Type 2) *vs*. 363 (spouses)	Insulin s.c., Insulin pump, OAD	Not reported	Self report	yes in type 1 diabetes, no in type 2 diabetes

insulin-treatment (n = 6204) or had oral hypoglycaemic agents (n = 877), the mean age of the patients was 43.6 years. As a reason for this finding, the authors discuss a selection bias (study based on members of the Danish Diabetes Association) and it can be speculated that such patients may have a higher degree of knowledge about their disease. They could be more likely to take appropriate steps before and while driving, such as blood glucose measurements before driving and counteracting traffic hypoglycaemias adequately.

Most of the preceding studies have typically focused on insulin treated patients to evaluate their traffic safety. Oral antidiabetic – and also potentially hypoglycaemia-inducing – drugs such as sulfonylureas or glinides were sparsely taken into consideration and were usually pooled, irrespective of whether they had hypoglycaemia-inducing properties or not. Given this focus on insulin therapy, it is furthermore surprising that the different regimens of insulin therapy are usually pooled and their differing potential to cause hypoglycaemias is not taken into consideration. This is why our own group [20] chose to study the incidence of symptomatic hypoglycaemia und hypoglycaemia-induced accidents during driving and to put this in relation to the different treatment modes of insulin therapy (conventional insulin treatment = CT, intensified conventional insulin treatment = ICT, continuous subcutaneous insulin infusion = CSII) as well as to those patients treated with oral hypoglycaemia-inducing agents (OAD).

In the study, we investigated 450 patients (122 treated with sulfonylureas, 151 with CT, 143 with ICT, and 34 with CSII) by an anonymous questionnaire at different locations to avoid bias. One-hundred and seventy-six persons had type 1 diabetes, 243 persons had type 2 diabetes, 31 subjects could not be classified. Based on the self-reporting questionnaires, we identified symptomatic hypoglycaemias during driving as rare events. Symptomatic hypoglycaemic events were investigated as events per 100 000 kilometers driven on the latest therapeutic regimen. The numbers were: OA: 0.19 ± 1.15; CT: 1.17 ± 6.56; ICT: 8.26 ± 35.60; CSII: 7.41 ± 16.60. The differences are significant; the only exceptions are the ICT and the CSII groups. If given as symptomatic hypoglycaemias per year driven on the latest therapeutic regimen, the numbers in the four different groups were: OA: 0.02 ± 0.12; CT: 0.06 ± 0.2; ICT: 0.63 ± 3.55; CSII: 0.37 ± 0.60. The differences were also significant except between the ICT and the CSII group. As can be seen, the incidence increases significantly with the degree of "strictness" between the treatment groups, except between the patients treated with ICT and CSII. Hypoglycaemia-induced accidents were rare at 0.01–0.49 if given as events per 100 000 kilometers, and 0.007–0.01 if given as events per year driven. These differences were not significant. As significant confounders influencing the traffic safety of the patients we identified age, duration of diabetes, and concomitant antihypertensive medication. Analyzing the data in accordance with the type of diabetes revealed a significantly higher rate of hypoglycaemic events in patients with type 1 diabetes. The number of hypoglycaemia-induced accidents was higher in this group, but failed slightly to reach statistical significance.

It is noteworthy that most of the patients in our study had had counselling concerning the disease (76.2 %), among them all patients treated with ICT and CSII, and thus they should have been able to handle hypoglycaemic events properly. We

regard this as the most likely explanation for the increasing number of hypoglycaemic events during driving with the rigidity of the four treatment groups, while there are no significant differences in the number of hypoglycaemia-induced accidents.

These findings may only reflect German realities. In an attempt to gain a picture of the European and US situation, Cox et al. [18] performed a study with an anonymous questionnaire in diabetes clinics in four European and seven US cities in patients with type 1 (n=313) and type 2 diabetes (n=274), as well as with non-diabetic spouse control subjects (n=326). Drivers with type 1 diabetes reported significantly more crashes, moving violations, episodes of hypoglycaemic stupor, requirement for assistance, and mild hypoglycaemia while driving as compared with type 2 diabetic drivers or spouse control subjects. Surprisingly, type 2 diabetic drivers had driving mishap rates similar to non-diabetic spouses. There were no salient differences between European and US drivers. In the case of the type 2 diabetic patients, the use of insulin or oral agents for treatment had no effect on the occurrence of driving mishaps. Crashes among type 1 diabetic drivers were associated with more frequent episodes of hypoglycaemic stupor while driving, less frequent blood glucose monitoring before driving, and the use of insulin injection therapy as compared with pump therapy.

Present state of traffic regulations

With this magnitude of studies failing to provide a clear and consistent picture of the traffic safety of diabetic patients under a possibly hypoglycaemia-inducing therapy, the policies of the licensing authorities and legal restrictions regarding diabetes and driving privileges vary throughout the world. Whereas many European authorities increasingly impose restrictions on driving motor vehicles, there seems to be a tendency towards a more moderate restriction policy in the US. It would go beyond the scope of this article to describe the situation in all countries. Thus, some examples of the legal principles and the clinical realities are given in the following.

United Kingdom

In the UK, diabetes is considered a prospective disability concerning the driver´s medical fitness. Consequently, patients under insulin treatment are usually issued a driving license for one to three years and must demonstrate adequate glycaemic control, and must be able to recognize warning symptoms of hypoglycaemia and meet visual standards. For people with type 2 diabetes who are controlled by diet or diet and tablets, there are no driving licence restrictions.

According to the road traffic act of 1988, diabetes mellitus is regarded as a prospective disability, which means that it is not necessarily at present – but may become – a condition affecting driving safety. No matter how the patient's diabetes is treated, he or she must inform the Driver and Vehicle Licensing Agency (DVLA) about this condition and the doctor must ensure the patient's awareness of their

respective health condition as well as adherence to recommendations for safe driving [21]. It is furthermore the duty of the doctor and it is left at his discretion to assess, who is at significant risk. These judgements may be a problem for clinicians, since they have a duty not only to the public, but to their patients as well. This may sometimes lead to discrepancies and a lack of consistency with the regulations by the DVLA [22]: A survey of 202 drivers with insulin-treated diabetes in the UK stated good compliance with statutory requirements to inform the licensing authority and motor insurer. One-hundred and ninety-five patients (96.5 %) were aware of their obligation to inform the DVLA of their insulin-treated diabetes and merely 12 of these had not done so. Flanagan et al. [22] also presented six "real life" case scenarios to consultant diabetologists, specialist registrars, and diabetes specialist nurses to investigate whether the advice given to patients by these different groups was consistent and in-line with the DVLA regulations. There was general agreement in the hypoglycaemia unawareness cases; however, there was considerable disagreement in the appraisal of whether patients were at risk of unstable control and should stop driving.

Compared to the 1970s, declaration rates for diabetes seem to have improved by far, probably as a result of local recommendations or those issued by principal charities such as Diabetes UK [23, 24]. In the UK, driving class 2 vehicles (large trucks and passenger vehicles) is barred to diabetic drivers on insulin. European law has recently extended this to so-called C1 (large vans and small lorries) and D1 (minibuses) vehicles, though the law has recently been revised to allow individual consideration for potential diabetic C1 drivers on insulin treatment [25].

European Union directive 91/439 states that diabetic patients who are using insulin are excluded from driving trucks, buses and heavy goods vehicles, except for small trucks in "very exceptional cases." Moreover, driving license authorities are supposed to instigate appraisal of the driving capacity of an applicant for a driving license if there is justified doubt about the driving capacity of the person concerned [26].

Netherlands

The Health Council of the Netherlands published a medical report in December 2002 [27] including a medical fitness-to-drive recommendation for people suffering from diabetes mellitus, applying to all types of driver licenses. This report provides guidelines for required ophthalmologic, cardiovascular and neurological examinations by a specialist. However, general restrictions for people suffering from diabetes mellitus cannot be applied and patients are personally responsible for reporting any changes in their medical condition.

Germany

As for Germany, the legal principles concerning traffic restrictions for diabetic persons have changed with European Union directive 91/439 of 1991: For motorcycles

and passenger cars, a medical examination will only be ordered if there is a specific reason. A vision test remains mandatory. In case of patients driving lorries and buses, there will be an initial appraisal and repeat appraisals as well. In the latter group, when being treated with insulin, a driving license is only given in a few extraordinary cases based on an extensive and detailed medical opinion. Repeat appraisals are also mandatory.

Besides the legal basis for evaluating the capacity to drive a motor vehicle, the appraisal guidelines established by the German Federal Ministry of Transport, Building and Housing are a set of rules intended to support the assessors in making decisions in individual cases [28]. These guidelines state that insulin-treated diabetic patients with good glycaemic control are able to drive passenger cars and motorcycles, unless they are apt to severe hypoglycaemias with loss of control and consciousness, as well as to hyperglycaemias with symptoms such as impairment of consciousness, debility, nausea and vomiting. This also includes patients treated with diet alone or oral antidiabetic drugs [29, 30].

USA

In the USA all states have individual licensing rules governing medical conditions that may apply to people with diabetes, as in the guidelines of the Federal Motor Carrier Safety Administration (FMSCSA) [31]. Special licensing rules can, for instance, include requirements for periodic medical evaluations from a physician and prohibitions on driving for a period of time after an episode of lost consciousness. These suggestions are sometimes a matter of debate, e.g., the FMCSA recently announced that an HbA1c between seven and 10 would be a desirable level in diabetic drug drivers. The rationale is that people with lower scores, who are aggressively managing their diabetes with insulin, may be more likely to have periods of very low blood sugar. However, insufficient gylcaemic control with a tendency towards hyperglycaemia would mean a higher risk for complications of the disease such as blindness, myocardial infarction or stroke [32].

Perspectives

Although many of the previously described studies failed to consistently demonstrate a higher incidence of traffic accidents in patients with diabetes mellitus compared to the general population, there is no doubt that hypoglycaemia during driving, and especially the unawareness [33] of such a situation, can end in life-threatening situations for the patient and other traffic participants. In a world-wide scale, the incidence of patients with diabetes mellitus is rising dramatically [34]. Furthermore, during the last decade, we have learned that it is an early onset of strict insulin therapy that helps to prevent, or at least delay, sequelae of the disease such as neuropathy, nephropathy, retinopathy, and cardiovascular disease. This strategy is more effective if tight, near-normoglycaemic control is achieved in type 1 dia-

betic patients [35], as well as in type 2 diabetics [36]. The price of tight glycaemic control is, of course, a rising number of hypoglycaemic episodes [37]. However, the improvement of glycaemic control can help societies significantly reduce the socioeconomic burden of the disease. With this in mind, it seems counterproductive and unjust to impose more and more restrictions, especially concerning participation in traffic, in insulin-treated patients. To protect societies from harm caused by an increasing number of diabetic drivers treated with potentially hypoglycaemia-inducing medication, the following problems need to be addressed and improved:

Ability to counteract hypoglycaemias

Patients need to have rapidly absorbable carbohydrates readily available in their car. A surprising finding in a study from 1980 by Clark et al. was that only 44 % of insulin-dependent diabetic drivers kept permanent energy sources in their vehicles (n = 157) [38]. Seven years later, in 266 patients with insulin-dependent diabetes, 77 % kept energy sources in their vehicles [39].

Although these were observations in a small and selected number of patients, the increasing number of diabetics who had counselling by health care professionals concerning their disease gives reason to expect a growing number will be aware of the problem. However, in 2003 the group of Cox et al. [40] reported that still one half of type 1 diabetic drivers and three quarters of type 2 diabetic drivers had never discussed hypoglycaemia and driving with their physicians.

Apart from professional patient education and individualised glycaemic goals, it goes without saying that every driver with a potentially hypoglycaemia-inducing treatment needs to carry rapidly absorbable carbohydrates for cases of emergency. Furthermore, patient empowerment, frequent self-monitoring of blood glucose, flexible insulin and other drug regimens, and ongoing professional guidance are crucial factors in the prevention of hypoglycaemia.

Decision to drive

Clarke et al. investigated the decision to drive at various blood glucose levels in type 1 diabetic subjects (n = 65 and n = 93) [41]. Although the results may not be applicable to all patients with insulin-treated diabetes, some findings were alarming:

Based on self-estimation by using a handheld computer to record data on symptoms, cognitive function, insulin dosage, food, activity, estimated and actual blood glucose levels, patients reported whether they would drive. The data were entered three to six times per day for a total of 50 to 70 collections per subject during a three to four week period. The patients stated that they would drive 43 % to 44 % of the time when they estimated their blood glucose level to be 3.3 to 3.9 mmol/L (60–70 mg/dL), and 38 % to 47 % of the time when their actual blood glucose level was less than 2.2 mmol/L (40 mg/dL). These observations suggest that persons with type 1 diabetes may not judge correctly when their blood glucose level is too low

to permit safe driving and may consider driving with a low BG level even when they are aware of the low level. Due to the relatively low level of low blood glucose level detection, the authors suggested that patients should measure their blood glucose level prior to driving.

Hypoglycaemia unawareness

The above mentioned study demonstrated a low level of detection of almost hypoglycaemic blood glucose levels in the type 1 diabetic group. Hypoglycaemia unawareness is not untypical in long-standing type 1 diabetes. Estimates are that hypoglycaemia unawareness currently affects about 25% of patients with type 1 diabetes [42, 43] It has also been demonstrated that the problem of hypoglycaemia unawareness is furthermore aggravated by alcohol consumption [44].

Hypoglycaemia unawareness may also be the case in insulin-treated type 2 diabetic patients with a long duration of the disease. Strategies to overcome hypoglycaemia unawareness include blood glucose awareness training (BGAT) [45, 46, 47]. BGAT is an eight-week psycho-educational training program for type 1 diabetic patients with goals of improving individual abilities to anticipate extreme blood glucose levels, detect the presence of extreme blood glucose levels, treat current extreme blood glucose levels, and prevent future extreme blood glucose levels. The training program follows an eight-chapter manual that includes didactic information, self-assessment tools, and active learning exercises. It is a well-documented training program for adults with type 1 diabetes and has repeatedly been re-evaluated. For example, in an improved version – the BGAT-2 – a total of 73 adults with type 1 diabetes participated in a six-month repeated baseline design with a 12-month follow-up. At six months and one month before BGAT-2 and at 6, and 12 months after BGAT-2, subjects used a handheld computer for 50 trials and completed psychological tests. From baseline to follow-up, BGAT-2 led to improved detection of hypoglycaemia and hyperglycaemia, improved judgment regarding when to lower high blood glucose, raise low blood glucose, and not to drive whilst hypoglycaemic. BGAT-2 also resulted in a reduction in occurrence of diabetic ketoacidosis, severe hypoglycaemia, and motor vehicle violations, and improvement in terms of worry about hypoglycaemia, quality of life, and diabetes knowledge.

Hyperglycaemia and traffic safety

Chronic and subchronic hyperglycaemia may also lead to a biochemical imbalance that may in turn affect driving performance and cause acute life-threatening events such as disorientation and decreased mental processing capacity that may also significantly impair a patient's ability to drive [48, 49]. Mild or moderate hyperglycaemia (10.5 mmol/l or 190 mg/dl) may not be that critical in terms of cognitive functions. During an euglycaemic clamp and a mildly hyperglycaemic clamp, Pais

et al. [50] were not able to demonstrate an impairment of cognitive functions as assessed by a word recall task test, and a modified Stroop task test. However, since hyperglycaemic situations are rather a consequence of omitting medication or patient incompliance, they are not within the focus of this article and literature is relatively rare.

Summary

Hypoglycaemic episodes during driving in diabetic patients with potentially hypoglycaemia-inducing agents do occur. Their incidence and consequences depend on the mode of therapy regimen, the frequency of blood glucose measurements, and factors such as age, comorbidities, further medication that may impair traffic vigilance such as antihypertensive drugs, and other well known culprits such as alcohol and drug consumption.

The consequences of traffic hypoglycaemias depend on patients' hypoglycaemia awareness, the ability to counteract hypoglycaemic events and external factors such as the degree of traffic, the vigilance of other road users, etc.

Although a magnitude of studies have investigated the traffic safety of diabetic patients, there is a tendency, but no clear evidence to show that, to date, patients with diabetes are significantly more involved in road traffic accidents than the population in general.

Since the consequences of his/her traffic performance may not only affect the diabetic driver him/herself, some relatively simple steps can help to reduce his/her traffic risk. Measuring blood glucose levels before and also during longer drives, especially in those who have lost the symptoms of low blood glucose and have a history of driving mishaps, is a diligent recommendation not only by health care professionals, but by diabetic patients themselves [51, 52].

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Drugs, Driving and Traffic Safety
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Changes in and predictors of driving after drug use and involvement in traffic crashes because of drugs, 1992–2005

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Abstract

This paper explores whether the proportions of U.S. adults who report driving after drug use and independent predictors of being in motor vehicle crashes under the influence of drugs have changed since 1991–1992. The National Longitudinal Alcohol Epidemiologic Survey (NLAES) and National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) involved face-to-face interviews with, respectively, 42 862 and 43 092 adults ages 18 and older in 1991–1992 and 2001–2002.

In both surveys, 66% ever drank alcohol, and 22% ever drove after drinking too much. In NLAES and NESARC, 16% and 21% ever used drugs, and 6% and 7% ever drove after drug use, respectively. In NLAES, nearly 4% were ever in a motor vehicle crash because of drinking, and 0.4% because of drug use, the respective equivalents of 8.5 million and 1 million people.

During the NLAES survey year, 44% of respondents drank alcohol, 5% drove after drinking too much, 5% used drugs, and 1% drove under the influence of drugs. In NESARC, the proportions were virtually identical.

NESARC re-interviewed 39 959 respondents in 2004–2005. One percent drove after drug use during the survey year, and one in five of them was in a crash while under the influence of drugs. Nineteen percent of those drivers were injured, and in 12% of the crashes someone else was injured.

In NLAES and NESARC, the strongest predictor of motor vehicle crash involvement under the influence of drugs was whether respondents experienced drug dependence, followed by alcohol dependence. The strongest independent predictors of having ever experienced drug dependence were early age of first drinking alcohol and having experienced alcohol dependence. Efforts to prevent drug-related motor vehicle crashes should include programs and policies that prevent and treat drug use as well as early alcohol use and alcohol dependence.

Introduction

Analyses of the National Longitudinal Alcohol Epidemiologic Survey (NLAES) [1] and National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) [2] found that earlier age of drinking onset was strongly related to experiencing alcohol dependence during one's life, as defined by the Diagnostic Statistical Manual of Mental Disorders (DSM-IV), fourth edition criteria. Longitudinal studies have identified this association [3, 4], as did a study of monozygotic twins discordant on age of first drinking alcohol [5], even though earlier work [6] suggested that, rather than reflecting a causal relationship, early age at first drink may be a marker for family or genetic liability to develop alcohol dependence. Persons ages 18–20 have the highest prevalence of alcohol dependence, followed closely by those ages 21–24 [7].

Cross-sectional NLAES analyses have also found that early age of drinking onset and personal history of alcohol dependence were independently associated with a greater likelihood of ever being in motor vehicle accidents after drinking, after controlling for binge drinking (5+drinks per occasion during the period respondents drank most), family history of alcoholism, demographic characteristics, and smoking and drug use history [8].

According to the NLAES conducted in 1991–1992, 7% of the U.S. population reported that they had driven after drug use, and nearly one percent reported being in a motor vehicle crash because of drug use [9]. This compares with 22% who drove after drinking and nearly 4% who were in a traffic crash because of drinking alcohol in the same time period [8].

The strongest predictors of ever being in a motor vehicle crash because of drug use were whether respondents were ever drug dependent and starting to use drugs at an early age. Whether respondents were ever alcohol dependent was also independently associated with having been in a motor vehicle crash because of drug use. Of note, the strongest predictors of starting to use drugs at an early age and having ever experienced drug dependence were starting to drink at an early age and whether respondents ever developed alcohol dependence [9].

The purpose of this article is to explore 1) whether the proportions of respondents in a national survey who drove after drug use have changed since 1991–1992, 2) whether the types of drugs consumed before driving and crash involvement have changed, and 3) whether the factors found to be the strongest predictors of being involved in motor vehicle crashes under the influence of drugs have changed.

Methods

In 1991–1992, under the direction of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the U.S. Census Bureau administered the NLAES, which involved face-to-face interviews with 42 862 respondents age 18 and older (mean age was 44) residing in the noninstitutionalized population of the United States.

The multi-stage sampling design has been described by Massey et al. [10]. Primary sampling units were stratified according to socio-economic criteria and selected with a probability proportional to their population size. Within primary sampling units, geographically defined secondary sampling units referred to as segments were selected systematically for the sample. The black population was oversampled at this stage to secure adequate numbers for analytic purposes. Segments were then divided into clusters of four to eight housing units, and all occupied housing units were included in the survey. Within each household, one randomly selected person age 18 or older was asked to participate. Young adults ages 18–29, a heavier drinking subgroup of the general population, were also oversampled. Weighting using SUDAAN in the analysis adjusted for the deliberate oversampling of black persons and persons ages 18–29 and accounted for the complex sampling design of NLAES. The household response rate for this representative sample of the U.S. population was 91.9%, and the sample person response rate was 90%.

In 2001–2002, NIAAA conducted NESARC under contract with the U.S. Census Bureau, and this also involved face-to-face interviews with a multi-stage probability sample of 43 093 adults ages 18 years and older (response rate 81%). The survey methods and other quality control procedures and test-retest reliability tests have been detailed by Grant et al [11].

From 2004 to 2005, the U.S. Census Bureau attempted to re-interview (wave 2) all eligible respondents from the 2001–2002 respondents (wave 1) who had not died, become incapacitated, become institutionalized, entered the military, or left the United States (N = 39 959). The interview rate among eligible respondents was 86.9%, yielding a sample of 34 653 U.S. adults and a cumulative response rate over the two surveys of 70.2%. Sample weights for the second survey were calculated to ensure that the weighted sample represents survivors of the original sample who remained in the noninstitutionalized population [12].

All potential NESARC respondents were informed in writing about the nature of the survey, the statistical uses of the data to be collected, the voluntary nature of their participation, and the federal laws that rigorously provide for the confidentiality of identifiable survey information. Only respondents consenting to participate after securing this information were interviewed. The research protocol for the initial NESARC survey and the follow-up survey (wave 2), including informed consent procedures, received full-ethical review and approval from the U.S. Census Bureau and the Office of Management and Budget.

Outcome Measures

In NLAES, respondents were asked “In your entire life, did you ever drive a car, motorcycle, truck, boat, or other vehicle when you were under the influence of a medicine or drug? Did you ever have a car, motorcycle, boat, or other accident because of your use of drugs? Did this happen in the last 12 months? During the last 12 months, which medicines or drugs did this happen with? Which medicines or drugs did this happen with more than once? Did this happen before

12 months ago? Which medicines or drugs did this happen with before 12 months ago?"

The following ten categories of drugs were mentioned: 1) sedatives, 2) tranquilizers, 3) pain killers, 4) stimulants, 5) marijuana, 6) cocaine or crack, 7) hallucinogens, 8) inhalants/solvents, 9) heroin, or 10) others. The age at first use of any drug, including painkillers, tranquilizers, or sedatives, without a prescription was classified as the earliest age at drug use.

In wave 1 of NESARC, respondents were asked "In your entire life, did you more than once drive a car, motorcycle, truck, boat, or other vehicle when you were under the influence of a medicine or drug? Did this happen in the last 12 months? During the last 12 months, which medicines or drugs did this happen with? Did this happen before 12 months ago? Which medicines or drugs did this happen with before 12 months ago?"

In wave 2 of NESARC, respondents were asked "Since the last interview, did you more than once drive a car, motorcycle, truck, boat, or other vehicle while you were under the influence of a medicine or drug? Did you drive a car, motorcycle, truck, or other vehicle and have an accident while you were under the influence of a medicine or drug? Did you drive a car, motorcycle, truck, or other vehicle and injure yourself in an accident while you were under the influence of a medicine or drug? Did you drive a car, motorcycle, truck, or other vehicle and injure someone else in an accident while you were under the influence of a medicine or drug?" Respondents were also asked if any of these events happened in the last 12 months and which medicines or drugs this happened with. In both waves 1 and 2 of NESARC, respondents were given a similar list of medicines and drugs as in NLAES to answer the survey questions.

Predictor variables

The age at drinking onset was ascertained by asking respondents: "About how old were you when you first started drinking, not counting small tastes or sips of alcohol?" This variable was classified as younger than age 14, 15, 16, 17, 18, 19, 20, and 21 or older. NLAES classified drinkers as those who had consumed at least 12 or more drinks during the past 12 months or a prior 12-month period (n = 27 616).

Measures of alcohol and drug use and dependence were derived from the Alcohol Use Disorders and Associated Disabilities Interview Schedule [13], a fully structured diagnostic psychiatric interview designed to be administered by trained interviewers who were not clinicians. The definition of lifetime dependence was based on the diagnostic criteria of DSM-IV [14]. The AUDADIS interview includes an extensive list of symptom questions to operationalize DSM-IV criteria for alcohol and drug dependence. Diagnosis of alcohol or drug dependence required that, in any one year, a respondent met at least three of seven criteria for dependence: (1) tolerance; (2) withdrawal; (3) persistent desire or unsuccessful attempts to cut down or stop drinking or drug use; (4) spending much time drinking, obtaining alcohol or drugs, or recovering from their effects; (5) giving up or reducing oc-

cupational, social, or recreational activities in favor of drinking or drug use; (6) impaired control over drinking or drug use; and (7) continuing to drink or use drugs despite a physical or psychological problem caused or exacerbated by drinking or drug use. Lifetime dependence meant a respondent had dependence in the past year or before the past year. The independent test-retest study conducted in the general population determined good reliabilities for past-year and before past year alcohol and drug use disorders, with κ's ranging from 0.62 to 0.76 and from 0.60 to 0.95, respectively [15].

Covariates

Other variables examined to determine whether they also predicted study outcomes included: age, gender, race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, other), education (less than high school education, high school graduate, associate's/technical degree or some other college, 4-year college graduate), marital status (married, never married, other), smoking status (smoked ≥100 cigarettes in the past 12 months, smoked ≥100 cigarettes in a prior 12-month period, never smoked ≥100 cigarettes), age at cigarette-use onset (<14, 14, 15, 16, 17, 18, 19, 20, ≥21, never), alcohol dependence and drug dependence (past 12 months, lifetime, never), history of depression before age 14, family history of alcoholism, and age at first drug use.

Statistical analyses

Like other analyses of NLAES, our statistical analyses were conducted using the SUDAAN statistical package [16] to account for the complex survey design and oversampling of NLAES in the examination of both effects and their standard errors.

First, we compared NLAES respondents and NESARC wave 1 respondents to assess the proportions of respondents who drove after using a medicine or drug and who did so after taking each medicine or drug listed above.

Second, among respondents age 21 and older in NLAES and NESARC wave 2, we compared the proportions who said they drove a car, motorcycle, truck, or other vehicle and had an accident under the influence of a medicine or drug in the past year among those listed above.

Third, we examined, among respondents who drank and who used drugs, which of these behaviors occurred first or whether both behaviors began the same year.

Fourth, among NESARC wave 2 respondents who ever drank, we conducted bivariate analyses using a modified test of independence that adjusts for sampling design to identify background and behavioral characteristics significantly associated with ever using drugs and ever being drug dependent. Then, among those who both drank and used drugs, we looked at what characteristics were significantly associated with driving after drug use and being in a motor vehicle crash under the

influence of drugs since the last interview, including age at drinking onset and having experienced alcohol or drug dependence.

Fifth, within the ever-drinker group, we conducted separate regression analyses to see if earlier age at drinking onset and ever experiencing alcohol dependence were each independently associated with a greater likelihood of ever using any type of drug, starting use at younger ages, and ever experiencing drug dependence. These analyses analytically controlled for respondent age, gender, education, marital status, past or current smoking, family history of alcoholism, and childhood depression. To assess the relationship between ages of drinking onset and drug use onset, we used a proportional odds model [17], which calculates the cumulative probabilities of the response categories of using drugs and using at an earlier age, compared with age at drinking onset. In this model, the response categories included never using drugs, initiation at ages 21 or older, initiation at yearly decrements until age 14, and initiation before age 14. These odds ratios (ORs) represent initiating drug use or, for those using drugs, initiating drug use at an earlier age. We adjusted this model for the same covariates as in the regression analyses.

Sixth, because only people who use drugs can drive under the influence of drugs, we focused on persons who ever drank and used drugs. We examined whether earlier age at drinking onset and drug use onset and experiencing alcohol and drug dependence between NESARC wave 1 and 2 were independently associated with driving under the influence of drugs and being in a motor vehicle crash under the influence of drugs between NESARC wave 1 and 2 after controlling for the factors previously cited.

In all the logistic regressions previously cited, we looked at the significance of relations between persons who began to drink at age 21 or older *versus* those who started at younger than or equal to age 14, 15–16, 17–18, and 19–20. ORs and 95% confidence intervals were calculated.

Results

According to the 1991–1992 NLAES, many people believe they have been in motor vehicle crashes specifically because of their drinking and drug use. In face-to-face interviews, 66% of respondents indicated that they ever drank alcohol (12+drinks in at least one year of their life) and 22% (35% of ever drinkers) reported ever driving after drinking too much. Of all respondents, 3.5% (16% of those who drove after drinking too much) reported they were in crashes because of their drinking, or the equivalent of 8.5 million people.

According to the same survey, a smaller percentage of respondents ever used drugs, 16%. However, among drug users a greater percentage ever drove under the influence of drugs (45% of ever drug users or 7% of the sample). A smaller percentage of those who drove after drug use, 6%, said they were ever in a crash because of their drug use, being 0.4% of the total sample, the equivalent about 1 million people nationwide. Of those who were ever in crashes as a result of drug

use, 57% had used marijuana before the crash, 27% used sedatives, 21% used cocaine, 18% used stimulants, 11% used tranquilizers, 10% used pain killers, 10% used heroine or methadone, and 7% used other drugs.

During the year of the NLAES survey, 44% of the sample drank alcohol. Five percent drove after drinking too much (11% of past year drinkers), and 0.2% (5% of those who ever drove after drinking too much) reported they were in crashes because they had too much to drink, representing about one half million people. In the year of the survey, 5% of the sample used drugs, and 1% drove under the influence of drugs (24% of past year drug users). In the past year, too few respondents were in a crash because of their drug use to make reliable percent and population estimates. Of drinkers who drove under the influence of drugs during the survey year, 83% had used marijuana before driving, 12% used cocaine, 8% used stimulants, 6% used sedatives, 6% used pain killers, 1% used heroine and tranquilizers, and 5% used another drug.

NESARC, the face-to-face national survey completed in 2001–2002, provides more contemporary information on the proportions of the U.S. adult population ages 18 and older who drive after alcohol or drug use. Sixty-six percent of respondents ever drank and 22% (35% of ever drinkers) said they more than once drove after drinking too much. These percentages are nearly identical to the NLAES results. The proportion who ever used drugs was greater in NESARC than NLAES, 21% *vs*. 16%. However, among drug users, a smaller percentage in NESARC than in NLAES drove after drug use, 28% *vs*. 45%, making the overall proportion of respondents who drove after drug use almost the same in both surveys, 6% and 7%, respectively. Of those who ever drove after drugs, 81% used marijuana, 9% used cocaine, 7% used amphetamines, and 4% used hallucinogens.

During the year of the NESARC survey, 44% of respondents drank alcohol, and 5% more than once drove after drinking too much (11% of past year drinkers or about 12 million people). During the year of the survey, 6% used drugs, and 1% (21% of past year drug users) more than once drove under the influence of drugs. These percentages are nearly identical to those reported in the 1991–1992 NLAES. Roughly 2.4 million people drove in the United States under the influence of drugs in the past year.

Of note, in NLAES among respondents who both drank and used drugs, 39% started drinking at least a year before they started using drugs, 29% started alcohol and drug use the same year, and 32% started drug use prior to drinking. In NESARC, 43% started drinking prior to drug use, 21% started both the same year, and 35% started drug use at least a year earlier than starting to drink. Also of note in the NLAES sample, more than 95% of persons who ever drove after drug use ever drank alcohol (in NESARC, over 98% did so).

In NESARC among persons who ever drove after drinking, 25% reported that they had also driven after drug use. In contrast, only 2% who never drove after drinking reported driving after drug use. During the year of the survey, 13% who drove after too much to drink also drove under the influence of drugs. However, less than 1% who did not drive after drinking drove after drug use in the past year. Of drinkers who drove under the influence of drugs during the survey year, 81%

Table 1 Characteristics of NESARC wave 2 ever drinkers who ever used drugs or were drug dependent, drove after drug use, or had a motor vehicle accident as a result of drug use.

	N = 34 629	Of All Drinkers†			N = 2876	Drank and Used Drugs Since the Last Interview	
		Ever Used Drugs (26 %, N = 8856)	Ever Drug Dependent (3 %, N = 1114)	Ever Drug Abuse (9 %, N = 2793)		Drove After Drugs (1 %, N = 738)	Motor Vehicle Accident After Drugs (< 1 %, N = 130)
Age at Drinking Onset							
≤14	2089	57%	16%	22%	904	33 %*	7%
15–16	4091	50	7	20	608	33	6
17–18	8508	34	3	11	877	28	5
19–20	4359	25	2	7	327	28	2
21+	10 926	13	1	3	570	18	5
Male	14 552	31	4	12	1550	32*	5
Female	20 077	22	2	6	1326	22	4
Age							
20–24	2159	40	8	15	505	37*	6
25–29	2730	35	5	12	406	28	4
30–34	3116	33	4	10	356	32	5
35–39	3505	33	4	11	296	25	6
40–49	7539	35	4	12	687	26	5
50+	15 580	15	1	4	626	19	4
Race/Ethnicity							
White	20 153	28	3	9	1801	28	5
Black	6580	23	3	7	471	30	5
Hispanic	6351	20	3	6	475	24	5
Other	1545	22	4	7	129	29	5

Table 1 *(continued)* Characteristics of NESARC wave 2 ever drinkers who ever used drugs or were drug dependent, drove after drug use, or had a motor vehicle accident as a result of drug use.

	N = 34 629	Of All Drinkers†			N = 2876	Drank and Used Drugs Since the Last Interview	
		Ever Used Drugs (26 %, N = 8856)	Ever Drug Dependent (3 %, N = 1114)	Ever Drug Abuse (9 %, N = 2793)		Drove After Drugs (1 %, N = 738)	Motor Vehicle Accident After Drugs (< 1 %, N = 130)
Education							
< High School	5510	20%	4%	7%	387	33 %*	7%*
High School	9448	23	3	8	734	31	7
College	15 188	30	4	10	1415	28	4
Graduate	4883	29	2	7	340	15	2
Married	17 784	24	2	8	978	22*	4*
Never Married	6617	35	6	12	1045	33	5
Other	10 228	27	4	9	853	29	7
Smoking							
Current	7929	44	8	17	1399	35*	7*
Former	356	36	6	12	46	43	3
Never	26 344	21	2	6	1431	20	3
Family History of Alcoholism							
Yes	12 245	36	6	12	1281	28	5
No	20 558	21	2	7	1441	28	5
Depression Before Age 14							
Yes	501	54	17	17	114	28	5
No	34 058	26	3	8	2756	28	5
Ever Alcohol							
Dependent	4908	63	15	25	1117	37*	7*
Abuse	6387	42	3	15	734	28	5
Neither	23 334	13	1	3	965	16	2

†All associations $p < 0.05$ *$p < 0.05$

Table 2 Predictors of drug use and starting drug use at young ages among NESARC respondents who ever drank.

	Drug Use and Starting Drug Use at Younger Ages*
Age Started to Drink	
≤14	2.41 (2.00, 2.89)
15–16	2.30 (1.99, 2.66)
17–18	1.80 (1.57, 2.07)
19–20	1.44 (1.23, 1.67)
21+	1.0
Ever Alcohol	
Dependent	4.61 (4.06, 5.25)
Abuse	2.67 (2.35, 3.03)
Never	1.0
Age	
20–24	3.35 (2.73, 4.10)
25–29	2.84 (2.39, 3.36)
30–34	2.34 (1.99, 2.75)
35–39	2.12 (1.81, 2.50)
40–49	2.36 (2.07, 2.70)
50+	1.0
Never Married	1.24 (1.09, 1.41)
Separated/Divorced	1.22 (1.09, 1.37)
Current Smoker	1.83 (1.64, 2.03)
Education	
<High School	1.0
College	1.43 (1.21, 1.69)
Graduate	1.70 (1.4, 2.07)
Family History of Alcoholism	1.48 (1.35, 1.62)

*Categories of this variable were: starting drug use at ages ≤14, 15–16, 17–18, 19–20, 21+, and never used drugs

used marijuana before driving, 13% used opiates, 9% used cocaine, 7% used amphetamines, 4% used tranquilizers, 4% used hallucinogens, 3% used sedatives, 1% used heroin, and 3% used another drug.

In NESARC wave 2, 4% of respondents and 7% of ever drinkers had used drugs in the past year, and 26% of the drug users had in the past year driven more than once after drug use, accounting for 1% of the total sample and 1.8% of drinkers. Of those who drove after drug use, 72% did so after marijuana use. Six percent of past year drug users and 25% of those who drove in the past year after drug use were in a motor vehicle crash after drug use since the previous interview. Five

percent of drug users and 20% of those who in the past year drove after drug use were in a motor vehicle crash in the past year under the influence of drugs (0.3% of the total sample and 0.4% of drinkers). Nineteen percent of the accidents after drug use resulted in an injury to the driver, and in 12% of the accidents someone else was injured. Of those in a crash in the past year because of drug use, 70% had used marijuana, 19% used opiates, 14% used amphetamines, and 9% used cocaine. However, because of the very small numbers, these percentages should be interpreted with caution. Table 1 provides information on characteristics associated with drug use, drug dependence, driving after drug use, and involvement in motor vehicle crashes under the influence of drugs since wave 1 of NESARC.

Logistic regression analyses focused on NESARC wave 2 and examined predictors of ever using drugs and starting drug use at an early age. Among persons who ever drank, the earlier respondents began to drink and whether they ever experienced alcohol dependence or abuse was associated with a greater likelihood of ever using drugs and starting drug use at an earlier age (Table 2). Other predictors of early drug use were being unmarried, a current smoker, having obtained a college and graduate education, and family history of alcoholism.

A second logistic regression also indicated that, among ever drinkers in wave 2, those who started to drink at an early age and those who had experienced alcohol dependence and abuse were more likely to have ever been drug dependent. Persons who started drinking at age 14 or less were 1.73 (1.32, 2.26) times more likely, and those starting at ages 15–16 were 1.3 (1.07, 1.57) times more likely than those starting to drink at age 21 or older to experience drug dependence. Respondents who ever experienced alcohol dependence were 3.80 (3.28, 4.39) times more likely and those who ever experienced alcohol abuse were 1.71 (1.47, 1.78) times more likely to have ever experienced drug dependence.

A third logistic regression examined predictors of experiencing drug dependence between the wave 1 and 2 NESARC surveys. Persons who were ever alcohol dependent were 2.05 (1.57, 2.67) times more likely to have been drug dependent between waves 1 and 2. Persons never married were 1.63 (1.29, 2.11) times more likely and those separated or divorced were 1.38 (1.03, 1.84) times more likely to have been drug dependent. Other predictors were having exhibited antisocial behaviors before age 15, while persons with graduate education were less likely to have experienced drug dependence.

A fourth logistic regression analysis of NESARC wave 2 revealed that drug dependence and abuse since the last interview were incredibly strong predictors of driving after drug use since the last interview. Persons who were drug dependent were 14.96 (7.71, 29.03) and drug abusers 9.26 (4.57, 18.74) times more likely than non-drug dependents or abusers to drive after drug use. Over 70% of persons who were drug dependent drove after drug use. Males were 1.63 (1.02, 2.62) times more likely, current smokers 1.5 (1.06, 2.22) times more likely, and former smokers 4.75 (1.52, 14.89) times more likely to have driven after drug use. Also, since the last interview, persons who experienced alcohol dependence were 1.45 (0.97, 2.19) times more likely and those who had experienced alcohol abuse were 2.47 (1.37, 4.43) times more likely to have driven after drugs since the last interview.

Having experienced drug dependence and abuse since the last interview were the strongest predictors of having been in a motor vehicle crash under the influence of drugs since the last interview. Persons who experienced drug dependence since the last interview were 14.96 (7.71, 29.03) times more likely and those who experienced drug abuse were 9.26 (4.57, 19.74) times more likely to have been in a crash after using drugs since the last interview than those who did no experience drug dependence or abuse. Alcohol abuse and dependence since the last interview were also independently associated with experiencing a crash after drug use since the last interview. Persons who experienced alcohol abuse since the last interview were 2.77 (1.53, 4.94) times more likely and those who were diagnosable with alcohol dependence were 1.77 (1.08, 2.89) times more likely to have been in a motor vehicle crash after drug use since the last interview.

Discussion

Analyses of the 2001–2002 NESARC and the 2004–2005 NESARC wave 2 national U.S. survey replicate many findings from the 1992–1993 NLAES national survey. In both NLAES and NESARC, larger proportions of respondents drove after drinking and were in crashes after drinking than drove after drug use or were in crashes under the influence of drugs. But the percentages of drinkers who ever drove after drug use were not inconsequential, being 6% and 7% in NLAES and NESARC, respectively. Just as in the 1991–1992 NLAES, the strongest independent predictor of being a driver in a motor vehicle crash after drug use during the time period between the 2001–2002 NESARC wave 1 survey and the 2004–2005 NESARC wave 2 survey was whether respondents experienced drug dependence during the same time period. Persons who experienced drug dependence between the two surveys were nearly 15 times more likely to have been a driver in a motor vehicle crash while under the influence of drugs. Those who met drug abuse diagnostic criteria during the same time period were nine times more likely to have been a driver in a drug-related crash between the two surveys.

Also, just as in the NLAES study more than one dozen years earlier, having experienced alcohol dependence between the two NESARC surveys was also significantly and independently associated with being a driver in a crash under the influence of drugs. Persons with alcohol dependence were twice as likely and those meeting alcohol abuse criteria were three times more likely to have been a driver in a crash after drug use.

As in the NLAES, among all respondents who ever drank alcohol, earlier age of drinking onset and having experienced alcohol dependence during one's lifetime were the strongest, significant, and independent predictors of whether respondents ever used illicit drugs and started using drugs at an early age. Persons who started drinking prior to age 17 were more than twice as likely to have used drugs, and persons who had experienced alcohol dependence were more than four times more likely to have used illicit drugs and started using drugs at an early age. Those who

were diagnosable with alcohol abuse were twice as likely to have used drugs and started using drugs at an early age.

Also, as in the NLAES survey, among respondents who ever drank alcohol, starting to drink at an early age and having experienced alcohol dependence (and abuse) were the strongest significant predictors of ever having experienced drug dependence. Persons ever alcohol dependent were 3.8 times more likely to have experienced drug dependence. Those who met alcohol abuse criteria were 1.7 times more likely to become drug dependent, as were persons who began drinking at age 14 or less. Those who started drinking at ages 15–16 were 1.3 times more likely to experience drug dependence, a significant association. This finding replicates previous research showing associations between early alcohol use and drug use [18–22] and development of drug dependence [23, 24].

Both early age at drinking onset and early drug use may share common genetic, environmental, and psychological antecedents with alcohol and drug dependence. This is consistent with problem behavior theory and subsequent research [25], which indicates that alcohol use and abuse at an early age do not usually occur in isolation but often occur with illicit drug use and a variety of other health-risk social problem behaviors. Also consistent with the problem behavior theory, Lo (2000) [21] postulated that the earlier individuals take their first drink, the more likely they are to be tolerant of deviant behavior. This can result in alcohol misuse and engagement in a variety of deviant behaviors. Lo also noted early age at drinking onset has been identified as an intervening or at least mediating variable that channels the effects on drug use of personality peer influence and parental impact [26, 27].

Several methodological factors should be considered when interpreting this study's results. First, this study was based on cross-sectional analyses of a self-report survey. Longitudinal studies are better able to identify the temporal sequence of associations. Self-report data may be subject to several biases. Respondents were asked to recall the ages that they first began to use alcohol and drugs. For older respondents, recall of events many years earlier may prove difficult. We repeated analyses focusing on individuals ages 18–34, in which recall might be less difficult, and found a similar pattern of results (data available on request). Among the younger respondents, the odds of persons who began drinking at a younger age using drugs and driving after drug use tended to be higher, as were the odds of drug- and alcohol-dependent persons driving after drug use in the past year and being in vehicular crashes because of drugs (data available on request).

Second, despite confidentiality assurances, some respondents may have been unwilling to disclose illegal behaviors, such as drinking at an early age, drug use, driving after drug use, or motor vehicle crash involvement because of drug use. On the other hand, those willing to admit drinking at an early age may also be more willing to admit these other behaviors.

Third, the wording of questions regarding driving after drinking and after drug use were slightly different in the NLAES and NESARC. For example, in NLAES respondents were asked "In your entire life did you ever drive a car, truck, boat, or other vehicle when you were under the influence of a medicine or drug? Did this happen in the past 12 months?" In NESARC, respondents were asked, "In your

entire life did you more than once drive a car, motor cycle, truck, boat, or other vehicle when you were under the influence of a medicine or drug? Did this happen in the last 12 months?" While it is unlikely that a large percentage of respondents drove only once under the influence of a drug, the NESARC wording may produce a slightly lower percentage who drove after drug use.

Also, in NLAES respondents were asked "Did you ever have a car, motorcycle, boat, or other accident because of your use of drugs?" In contrast, NESARC asked "Did you drive a car, motorcycle, truck, or other vehicle and have an accident while you were under the influence of a medicine or drug?" It is possible that the NLAES question might yield a slightly lower reporting percentage of drug-related motor vehicle accidents. In NLAES, 1 in 100 who drove after drug use in the past year reported being in a crash because of drug use, whereas in NESARC wave 2 14 % who drove after drug use were in a crash after drug use in the past year. Regardless of the wording, however, less than 1 % of respondents reported being in a crash after drug use during the year of the respective surveys.

Fourth, although some respondents said the motor vehicle crashes they experienced were because of their drug use, it is impossible to ascertain whether drug use was the sole cause. The survey did not ask these respondents if they also had been drinking before the crash or whether they were speeding or driving recklessly. Why they thought their drug use caused the crash was not explored. Nonetheless, it is fair to assume they had, indeed, used drugs before the crash.

Perhaps a more objective set of questions would have asked respondents if they consumed drugs within a specific period before the crash. Studies need to compare the proportion of persons in crashes who test positive for the presence of drugs and/or alcohol with the proportions among persons not in crashes who drive at similar times and locations. Case crossover designs can also help explore these potential relations.

Also, the survey instruments in NLAES and NESARC did not examine crashes that did not involve alcohol or drugs. Therefore, the relative likelihood of nonsubstance users' crash involvement could not be compared with that of drinkers and drug users. In addition, the involvement of drinkers and drug users in crashes not involving alcohol and drugs could not be determined. Future studies should make such comparisons.

If case control studies show elevated fatal crash risk for persons who drive after using drugs and drugs and alcohol in combination, then that will provide a rationale for comprehensive testing of all fatally injured drivers for these substances. Part of the reason for the strong progress during the past two decades in reducing alcohol-related fatal crashes in the United States was the comprehensive testing of the blood alcohol content of fatally injured drivers in traffic crashes. This permitted researchers to conduct studies comparing pre- and post-law trends in alcohol- and nonalcohol-related fatal crashes in states that passed laws to reduce alcohol-related fatal crashes, such as laws that raised the minimum legal drinking age, *per se* laws, administrative license revocation, and lower legal blood alcohol limits. Trends in those states could be compared with trends in states that did not enact such legislation [28].

Similarly, if states start to enact new drug driving laws, comprehensive testing will be needed to assess whether the laws produce reductions in drug driving fatal crashes as well as alcohol-related fatal crashes. Studies of new legislation to reduce alcohol-related fatal crashes will not only have to consider potential confounding effects of other pre-existing drinking and driving laws and alcohol policies, but also drug driving laws, particularly those enacted in close temporal proximity to the drinking and driving laws. [28].

The results of this study point to a need to further explore why people who start drinking at early ages and who have been alcohol dependent are more likely to use drugs and develop drug dependence. Although in both NLAES and NESARC most who both drank and used drugs began to drink before they used drugs or began both behaviors during the same year, some respondents started drug use at least a year before they began drinking. These respondents may have driven after drug use and experienced drug-related motor vehicle crashes even before they began drinking or developed alcohol dependence. It is also possible that genetics, personal psychological characteristics, peer pressure, family environment, community, and other factors may predispose some youths to engage in a variety of risky behaviors, such as early drinking and drug use onset, driving after drinking and drug use, and other reckless driving behaviors.

Nonetheless, our results suggest that, although less frequent than driving after drinking, driving under the influence of drugs is not a rare, isolated behavior and that drinkers who start at an early age and develop alcohol dependence were more apt to use drugs and develop drug dependence. In turn, among persons who have both consumed alcohol and drugs, having experienced drug and alcohol dependence were each independently associated with having driven under the influence of drugs and ever having been in crashes after drug use.

Most states legally require people convicted of driving under the influence of alcohol to be assessed for alcohol use disorders and to receive treatment [29]. Laws that mandate screening and counseling for both alcohol and drug use among persons convicted of either driving after drinking or after drug use or both also need to be evaluated. Screening, brief intervention, and treatment studies both within the context of legal actions against impaired drivers and in trauma centers and emergency departments should follow over time the driver records of persons offered and not offered alcohol and drug counseling to test whether these screening and treatment programs produce greater declines in alcohol and other drug use and, in turn, greater declines in motor vehicle crashes involving driver use of alcohol and other drugs.

Alcohol treatment studies have shown higher rates of improvement among persons with co-existing alcohol and drug problems if both alcohol and drug use are addressed in treatment [30]. The effects of screening those convicted of driving after drinking for illicit drug use problems and of addressing drug problems should be explored. Some research studies in emergency departments and trauma centers have shown screening and brief interventions can reduce driving after drinking [31–33] and drug use [34]. The effects of screening and brief interventions on driving after drug use and drug-related crash involvement should be explored. The effects

of screening and brief intervention for alcohol and other substance use problems outside the criminal justice system warrants study because most drivers in alcohol-related fatal crashes have never been convicted of driving under the influence. Most states have laws that allow insurance companies to withhold medical reimbursement for treatment of people injured under the influence of alcohol or drugs. Such laws may have deterred some medical providers from screening persons injured in motor vehicle crashes for alcohol and drug use. Whether repeal of those laws, as has occurred recently in a few states, will foster more screening for alcohol and drug misuse in emergency departments and primary care settings and, in turn, produce reductions in alcohol- and drug-related traffic crashes is an important research question with considerable potential public health and traffic safety significance.

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Drugs, Driving and Traffic Safety
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Reducing illegal blood alcohol limits for driving: effects on traffic safety

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Abstract

This chapter provides a scientific review of the evidence regarding the benefits of reducing the illegal blood alcohol concentration (BAC) limit for driving. Numerous independent studies in the United States indicate that lowering the illegal BAC limit from 0.10 to 0.08 g/dL has resulted in 5 to 16% reductions in alcohol-related crashes, fatalities, or injuries. The illegal limit is 0.05 BAC in numerous countries around the world and several international studies indicate that lowering the illegal *per se* limit from 0.08 to 0.05 g/dL BAC also reduces alcohol-related fatalities. Laboratory studies indicate that impairment in critical driving functions begins at low BACs and that most subjects are significantly impaired at 0.05 g/dL BAC. The relative risk of being involved in a fatal crash as a driver is four to 10 times greater for drivers with BACs between 0.05 and 0.07 g/dL compared to drivers with 0.00 g/dL BACs. There is strong evidence in the literature that lowering the BAC limit from 0.10 to 0.08 g/dL is effective, that lowering the BAC limit from 0.08 to 0.05 is effective, that lowering the limit from 0.05 to 0.03 or 0.02 g/dL is effective, and that lowering the BAC limit for youth to any measurable amount of alcohol is effective. These law changes serve as a general deterrent to drinking and driving and ultimately save lives. This critical review supports the adoption of lower illegal BAC limits for driving in countries around the world.

Introduction

The international trend toward lowering BAC (blood alcohol concentration) limits has been continuing for some time now, with most industrialized nations reducing their illegal limit to a BAC of 0.05 or lower. The illegal limit is 0.05 g/dL BAC in Australia, Austria, Belgium, Bulgaria, Croatia, Denmark, Finland, France, Germany, Greece, Israel, Italy, the Netherlands, Portugal, South Africa, Spain, and Turkey, as examples. Japan and Poland recently adopted a 0.03 g/dL BAC standard. Norway, Russia, and Sweden have essentially a zero-tolerance limit of 0.02

g/dL BAC. This trend has not developed without merit; a myriad of studies have indicated that lowering illegal BAC limits is in the best interest of the public. For example, laboratory studies indicate that impairment in critical driving functions begins at low BACs [1, 2]. Most subjects in laboratory studies are significantly impaired regarding visual acuity, vigilance, drowsiness, psychomotor skills, and information processing by the time they reach 0.05 g/dL BAC compared to their performance at 0.00 g/dL BAC [3]. The relative risk of being involved in a fatal crash as a driver is four to 10 times greater for drivers with BACs between 0.05 and 0.07 g/dL, compared to drivers with 0.00 g/dL BACs [4]. A recent study sponsored by the National Highway Traffic Safety Administration (NHTSA) in the United States indicates that drivers at 0.04 g/dL BAC have a significantly higher relative risk (ratio of 1.18 to 1.00) of being involved in a traffic crash than drivers at 0.00 g/dL BAC [5, 6]. Leading medical, crash prevention, public health, and traffic safety organizations around the world support BAC limits at 0.05 g/dL or lower, including the World Medical Association, the American and British Medical Associations, the European Commission, the European Transport Safety Council, the World Health Organization, and the American College of Emergency Physicians [7].

This chapter provides a critical review of the evidence regarding the potential benefits of enacting lower BAC *per se* limits in countries around the world. The first section of the chapter discusses methodologies used in evaluating the effects of laws of this nature. The second section summarizes the evidence from the United States for lowering the BAC limit from 0.10 to 0.08 g/dL. The third section covers the available evidence for lowering the BAC limit to 0.05 g/dL. The fourth section describes a few studies of lowering the BAC from 0.05 to 0.03 or 0.02 g/dL. The fifth section reviews the evidence for lowering the BAC limits for drivers younger than age 21. The sixth section discusses the evidence for lowering the BAC limit for motorcycle riders and convicted driving while intoxicated (DWI) offenders. The last section concludes that lowering BAC limits is an effective strategy to reduce alcohol impaired-driving casualties.

Discussion of methodologically rigorous studies

The effectiveness of any law is highly dependent on the extent to which it is enforced and the intensity and publicity surrounding that enforcement. When an evaluation of a new impaired-driving law is conducted, it is difficult to control for variations in enforcement activities, variations in public awareness, changes in other laws, and changes in alcohol consumption – all of which could affect the outcome. When researchers study multiple applications of the same law, there almost always are cases where one or two of the countries or jurisdictions will show no benefit or might even experience an increase in some measure of impaired driving. These exceptions to the more general finding of a benefit often will be seized by critics for use in opposing the policy. Thus, it is important to consider the preponderance of evidence provided by all the available research.

New public health programs and policies experience several developmental phases before reaching full implementation throughout a country [8]. For example, Canada adopted its current 0.08 g/dL BAC Criminal Code limit in 1969, whereas in the United States, Utah, and Oregon were the first two states to lower their illegal limit from 0.10 to 0.08 g/dL *per se* BAC in 1983. By 1999, 18 states and the District of Columbia had lowered the illegal limit from 0.10 to 0.08 g/dL BAC. During that time, nine evaluations of 0.08 laws involving 11 states had already been conducted in the United States. A scientific review by a committee of experts assembled by the U.S. Centers for Disease Control (CDC) indicated that the median effect detected by the studies of 0.08 g/dL BAC that were reviewed was a 7% reduction in alcohol-related fatal crashes [9]. The evidence for the effectiveness of lowering the illegal BAC limit produced a consensus among highway safety advocates on the value of the 0.08 law in the United States. This consensus resulted in the U.S. Congress providing a sanction that withheld a portion of a state's highway construction funds for states not adopting 0.08 laws by October 1, 2003.

Studies of the effects of lowering BAC limits around the world have employed various research designs and methodologies. The effectiveness measure and the analysis procedure have varied from study to study. Contemporaneous changes in other laws and policies, such as the enactment of an administrative license suspension (ALS) or administrative license revocation (ALR) law permitting officers to seize the licenses of impaired drivers at the time of arrest, or the introduction of random roadside breath testing (RBT) enforcement activities, were not fully considered in some of the studies. A review by the U.S. General Accounting Office [10] concluded after a review of the research that the 0.08 law was effective, but generally only when combined with the adoption of an ALS/ALR law. To test the significance of the ALS/ALR law in conjunction with a 0.08 BAC law, Hingson, Heeren, and Winter [11] compared states in which the two laws were implemented at about the same time with states where an ALS/ALR law had been in place for some time before adoption of a 0.08 law. They found that the 0.08 law made a significant difference in states where the ALS/ALR law had been in place for some years.

Because of differences in effectiveness measures or analytical techniques, Foss, Stewart, and Reinfurt [12] found no significant change because of the 0.08 law in North Carolina, whereas Apsler, Char, Harding, and Klein [13] did find a significant reduction in alcohol-related crashes in North Carolina associated with the 0.08 BAC law. Research and Evaluation Associates (REA) [14] reported a reduction in alcohol-related fatal crashes in California; conversely, Rogers [15], in a later analysis, did not find a significant reduction in fatal crashes in California attributable to the 0.08 law but instead found a reduction in nighttime injury crashes in California due to the 0.08 law.

Voas, Tippetts, and Fell [16] considered the 0.08 g/dL BAC law as one of several alcohol safety measures in a study that included all 50 states plus the District of Columbia over a 16-year period. This study, which applied a common methodology to all the states from 1982 to 1997, found an 8% treatment effect of the 0.08 BAC law. The finding was very similar to the Centers for Disease Control and Prevention (CDC) [9] finding of a 7% median treatment effect. The Voas et al. [16] study was

the most comprehensive study of lower BAC limits up to that date and did control for many potentially confounding factors such as ALR, safety belt legislation and the economy. Since then, Wagenaar, Maldonado-Molina, Ma, Tobler, and Komro [17] published an even more comprehensive study of 0.08 BAC and other laws which will be described later.

A significant limitation in the interpretation of all field studies of the implementation of new laws is the varying analytical methods and criterion measures used by different investigators. With this in mind, Tippetts, Voas, Fell, and Nichols [18] conducted identical individual analyses of 19 U.S. jurisdictions with 0.08 laws using a common dataset, the same effect measure, and an identical analytical procedure. This permitted a more direct comparison of the effectiveness of the 0.08 law in each jurisdiction where it was implemented and supported a meta-analysis of the effect sizes in each of the 19 jurisdictions to derive an overall effectiveness measure for the 0.08 law. The meta-analysis provided an estimate that the enactment of laws lowering the BAC limit from 0.10 to 0.08 g/dL reduced the proportion of drivers in fatal crashes who were drinking by 14.8%. Based on this reduction, had the other U.S. states adopted a 0.08 law in 2000, 947 lives might have been saved. Bernat, Dunsmuir, and Wagenaar [19] examined the effects of 0.08 BAC laws in the same 19 jurisdictions using changes in single-vehicle nighttime (SVN) fatal crashes (when alcohol is most likely a factor) as their measure. SVN fatal crashes is a common surrogate measure of alcohol involvement but is not as sensitive as the measure used by Tippetts and colleagues [18]. The mixed-model regression analyses showed a significant 5.2% reduction in SVN fatal crashes associated with the 0.08 BAC law across all states after adjusting for ALS/ALR and trends. Wagenaar and colleagues [17] determined the effects of lowering the BAC limit in 28 states between 1976 and 2002 using an interrupted time series quasi-experimental design. They concluded that lowering the BAC limits in those states resulted in significant reductions in single vehicle nighttime (SVN) fatal crashes and fatal crashes with drivers at low, medium, and high BAC levels. These methodologically rigorous studies verified that lowering the illegal BAC limit from 0.10 to 0.08 g/dL in the United States has had a significant safety impact.

A summary of the evidence for lowering the BAC limit from 0.10 to 0.08 g/dL

At the start of the 1970s, when the first U.S. national effort at controlling alcohol-impaired driving began, most states based their impaired driving laws on the driver's behavior and the BACs' of drivers at which it was "presumed" that a person was intoxicated. The presumption could be rebutted by other evidence. These presumptive levels were generally set at 0.15 BAC, although a few states had BAC levels of 0.12 or 0.10. Beginning in the 1970s, the U.S. Department of Transportation (USDOT) used its authority under the Highway Safety Act of 1966 to encourage all states to adopt 0.10 BAC as the level for intoxicated or impaired driving.

The USDOT also urged the states to enact laws that made it a violation *per se* to drive with a BAC of 0.10 or higher. From the outset of the movement to adopt 0.10 BAC as the national standard, there were advocates for even lower BAC levels. By 1983, this sentiment had resulted in the enactment of 0.08 BAC *per se* laws in the States of Oregon and Utah. A strong grassroots movement started in the early 1980s that has had a significant effect on United States laws, including 0.08 BAC laws. The most visible organization in this movement was Mothers Against Drunk Driving (MADD), founded in the United States in 1980 by a mother whose 13-year-old daughter had been killed by a hit-and-run driver with a long record of alcohol offenses. In 1986, the USDOT took its first formal step toward advocating a lower illegal limit by including a 0.08 BAC law as one of the regulatory criteria for a supplemental alcohol traffic-safety grant under the program authorized by the U.S. Congress (23 U.S.C. 408).

In 1988, NHTSA released a review of the scientific literature on the impairment of driving-related skills at low BACs, based on laboratory testing of dosed subjects [20]. This report documented that impairment of driving-related skills starts at very low BACs, for some as low as 0.02 g/dL BAC. Additional states began to consider 0.08 g/dL BAC *per se* levels, and three more states adopted the new level: Maine in 1988, California in 1990, and Vermont in 1991. California's 1990 legislation lowered the state's *per se* limit from 0.10 to 0.08 g/dL BAC and established an ALR law a short time later. In 1991, NHTSA sponsored a study of the effects of these new laws in California and found that the lower BAC level and the new ALR law in combination resulted in a 12% decrease in alcohol-related fatalities [14].

Between 1992 and 1998, 10 additional states in the United States adopted 0.08 BAC *per se* laws: Kansas and North Carolina (1993); Florida, New Hampshire, New Mexico, and Virginia (1994); Alabama and Hawaii (1995); and Idaho and Illinois (1997). The movement toward a national standard for 0.08 g/dL BAC received renewed attention in the 105th Congress. On June 15, 2000, the Senate passed H.R. 4475 (the DOT Appropriations Bill for FY 2001) that included a general provision encouraging states to adopt 0.08 BAC laws by withholding a portion of a state's federal highway funds, beginning in FY 2004, for states that do not adopt 0.08 g/dL. The final 0.08 BAC bill (Section 351) was adopted by Congress and signed by the President shortly after that.

The following early studies of the impact of lowering the BAC limit to 0.08 g/dL were conducted before 1999:

- An NHTSA study of the California 0.08 BAC law [14].
- An NHTSA staff study of California, Maine, Oregon, Utah, and Vermont, five of the first states to enact 0.08 BAC laws [21].
- A California Department of Motor Vehicles study of its 0.08 BAC and ALR laws [15].
- A Boston University study of the five early states to enact 0.08 BAC laws [22].

These studies controlled for some extraneous factors and provided initial evidence of the benefit of 0.08 BAC laws on alcohol-related crashes. One factor that was confounded in these studies was the possible interaction of 0.08 BAC and ALR laws enacted in close temporal proximity in some states. However, these studies pro-

vided credible evidence of the impact of the 0.08 law, particularly in combination with the ALR law. NHTSA recognized the need for more replications on which to base conclusions.

In the Johnson and Fell [21] study, it is noteworthy that of the 30 different measures used to determine effectiveness of the 0.08 BAC law in five states (six measures in each state), 26 of the measures showed decreases, with 10 of the decreases showing statistical significance. Sixteen of the 20 changes in the measures that were not statistically significant were decreases. Thus, this early study showed *directional* changes that were indicative of 0.08 g/dL BAC having an effect. This finding was very similar to findings of the effects of ALR [23, 24] and minimum legal drinking age of 21 in the United States [25].

Additional studies of the effects of lowering the limit to 0.08 g/dL BAC were sponsored and released by NHTSA in early 1999:

- A study of North Carolina's 0.08 BAC law [12]
- A study of 11 states with 0.08 BAC laws [13]
- A 50-state study of three important impaired-driving laws – ALR, 0.08 g/dL BAC, and zero tolerance for youth [26; see also 16]

The results of these studies of the 0.08 BAC laws' effects provided additional evidence to support the effectiveness of 0.08 BAC laws. The 50-state study showed a significant (8%) reduction in the involvement of low- and high-BAC drivers in fatal crashes. The 11-state study found that 0.08 BAC laws were associated with reductions in alcohol-related fatalities in seven of the 11 states studied, either alone or in conjunction with ALR laws. Also in this study, 32 of 39 outcomes directionally supported the conclusion that 0.08 BAC laws, when added to existing laws and programs, were associated with reductions in alcohol-related traffic fatalities. The North Carolina study found no clear effect of its 0.08 BAC law. However, several of the study's outcomes were directionally consistent with suggesting that the law had an effect greater than the decline in alcohol-related fatalities that began before 0.08 g/dL BAC was enacted.

Hingson, Heeren, and Winter [11] analyzed the effectiveness of 0.08 BAC laws in six states enacting 0.08 laws in 1993 and 1994. They found an overall 6% reduction in alcohol-related deaths in these six states and estimated that 400 to 500 additional lives could be saved each year if every state had had a 0.08 BAC law. This study took into account many of the criticisms of previous studies by the same authors. Two other studies of the effectiveness of lowering the illegal BAC limit to 0.08 g/dL appeared in the literature about the same time [27, 28]. Dee used somewhat novel, panel-based evaluations of 0.08 laws, which in many respects addressed methodological limitations of previous studies. Fourteen states that adopted 0.08 BAC laws between 1982 and 1998 were analyzed and compared to the rest of the states that did not adopt 0.08 laws using traffic fatality rates as the key measure. Alaska, Hawaii, and the District of Columbia were excluded from the analyses because of small sample sizes. The regression analyses controlled for the potential effects of 0.10 BAC laws, ALR laws, dram shop laws, mandatory jail time for first DUI offenses, zero-tolerance laws for youth, mandatory seat belt laws (primary and secondary enforcement, separately), raising the speed limit on interstate high-

ways to 65 and 70 miles per hour (mph), vehicle miles traveled in the state, state unemployment rate, and state personal income per capita. A statistically significant reduction of 7.2% in traffic fatality rates was associated with the adoption of 0.08 BAC laws. Dee estimated that 1200 lives could be saved annually if the additional 23 states with ALR laws also adopted 0.08 BAC laws.

Eisenberg [28] conducted a baseline analysis of the effects of 0.08 laws similar to that of Dee [27], but with the addition of controls for graduated driver licensing (GDL) laws and the presence of MADD activities in the state. Eisenberg's analysis showed that the 0.08 g/dL BAC limit was associated with a 5% reduction in the mean traffic fatality rate and that 0.10 BAC limit laws were associated with a 2.4% reduction. This estimate suggested that lowering the limit from 0.10 BAC to 0.08 g/dL would garner a further reduction of 2.6% in the mean total fatal crash rate. This was a statistically significant reduction ($p < 0.05$) even though it was a modest reduction.

Two of the most current studies of the effectiveness of 0.08 BAC laws were discussed in the first section [18, 19]. Kerr, Greenfield, and Midanik [29] used a totally different measure of the effectiveness of laws – the reported number of drinks it takes to "feel drunk" from National Alcohol Surveys. Their study showed that the average number of drinks that it takes to "feel drunk" declined significantly between 1979, 1995 and 2000 (from 9.76 drinks for males in 1979 to 7.49 in 1995 to 6.63 in 2000) associated with the adoption of 0.08 BAC laws. Gorman, Huber, and Carozza [30], on the other hand, could not find any significant effects on alcohol-related crashes or fatalities due to the 0.08 BAC law in Texas. Finally, Wagenaar and his colleagues [17] did find direct effects of lowering the BAC limits in 28 states and estimated that 360 deaths were prevented by the 0.08 BAC law and that an additional 538 lives could be saved if the United States lowered their BAC limit to 0.05 g/dL BAC.

Studies of impairment and crash risk at 0.08 g/dL BAC

A 1988 review of 177 studies clearly documented significant impairment at 0.08 g/dL BAC [20], and a 2000 review of 112 more recent studies provided even stronger evidence of impairment at 0.08 g/dL BAC [2]. Together, these two reviews have summarized the findings of nearly 300 studies of impairment at low-BAC levels, and the findings are remarkably consistent. A comprehensive laboratory study examined driving skills among 168 subjects of both sexes and various ages and drinking histories [3]. This study not only confirmed significant impairment in all measures of performance at a 0.08 g/dL BAC, but also found that impairment was present in relatively consistent levels across all age groups, sexes, and drinker types [3]. An epidemiological study, which compared data from a national roadside survey with data from all drivers involved in fatal crashes over two years, showed that the risk of being killed in a single-vehicle fatal crash at 0.08 g/dL BAC is 11 to 52 times greater than at 0.00 g/dL BAC. That same study indicated that the risk of dying in a single-vehicle crash at 0.05 g/dL BAC was four to 17 times that of drivers at 0.00 g/dL BAC [4]. Earlier, Ferrara et al. [1] concluded in their review article that changes in driving performance begin with any departure from 0.00 g/dL BAC.

Summary of 0.08 BAC laws

Figure 1 (an update of Shults et al. [9], Fig. 2) summarizes the effectiveness of 0.08 laws in graphic form. It shows a consistency and direction in the change in alcohol-related traffic fatalities that has occurred after 0.08 laws were adopted in the various states.

Table 1 summarizes all of the studies of the effectiveness of 0.08 BAC laws in the United States.

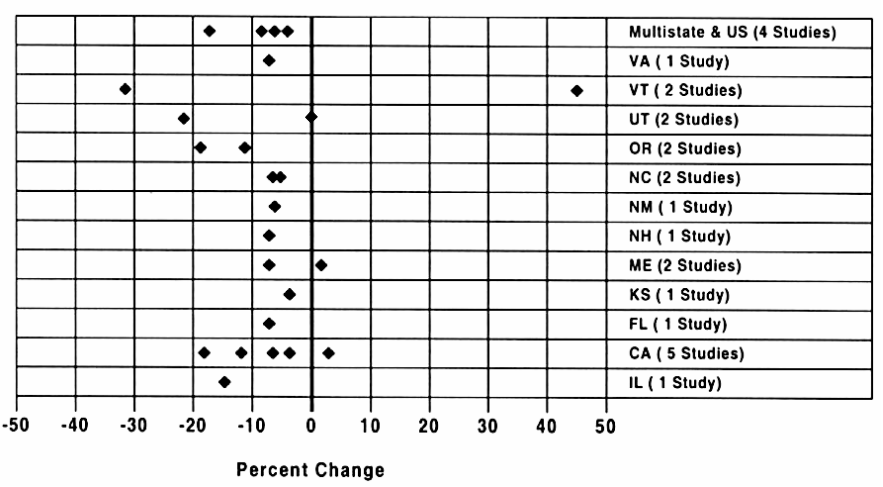

Figure 1 Percentage of change in alcohol-involved motor vehicle fatalities following enactment of 0.08 laws in the United States.

Table 1 Studies of the effects of lowering the illegal BAC limit from 0.10 to 0.08 g/dL in the United States.

Study	Results
Research and Evaluation Associates (1991) [14] "The Effects Following the Implementation of an 0.08 BAC Limit and an Administrative *Per Se* Law in California"	12% reduction in alcohol-related traffic fatalities associated with the 0.08 and ALR laws.
Johnson and Fell (1995) [21] "The Impact of Lowering the Illegal BAC Limit to 0.08 in Five States in the U.S."	Significant reductions in alcohol-related fatal crashes in four of five states ranging from 4 to 40%.

Table 1 (*continued*) Studies of the effects of lowering the illegal BAC limit from 0.10 to 0.08 g/dL in the United States

Study	Results
Rogers (1995) [15] "The General Deterrent Impact of California's 0.08% BAC Limit and Administrative *Per Se* License Suspension Laws"	Seven-percent reduction in nighttime fatal and serious injury crashes. No significant decrease in alcohol-related fatal crashes.
Hingson et al. (1996) [22] "Lowering State Legal Blood Alcohol Limits to 0.08 Percent: The Effect on Fatal Motor Vehicle Crashes"	16 to 18% reduction in proportion of fatal crashes involving fatally injured drivers with BACs ≥0.08 and ≥0.15 g/dL.
Apsler et al. (1999) [13] "The Effects of 0.08 BAC Laws"	The 0.08 BAC law is associated with significant reductions in alcohol-related fatal crashes, alone or in conjunction with ALR, in seven of 11 states.
Foss et al. (1999) [12] "Evaluation of the Effects of North Carolina's 0.08% BAC Law"	No clear effect of 0.08 BAC law on already declining alcohol-related fatalities.
Voas et al. (2000) [16] "The Relationship of Alcohol Safety Laws to Drinking Drivers in Fatal Crashes."	The 0.08 BAC laws are associated with 8% reduction in fatal crashes involving drinking drivers. If all states adopt a 0.08 g/dL BAC, an estimated 590 lives could be saved each year.
Hingson et al. (2000) [11] "Effects of Recent 0.08% Legal Blood Alcohol Limits on Fatal Crash Involvement."	Six-percent reduction in alcohol-related fatal crashes associated with 0.08 BAC laws in six states. If all states adopt 0.08 g/dL BAC, an estimated 400 to 500 lives could be saved each year.
Voas et al. (2000) [31] "Effectiveness of the Illinois 0.08 BAC Law" Also see Voas, Tippetts and Taylor (2001) [32] "Effectiveness of the Illinois 0.08 Law: An Update with the 1999 FARS Data"	The 0.08 law reduced the number of drinking drivers in fatal crashes by 13.7% in first 12 months. Followup study confirmed 13.7% reduction over 30 months after 0.08 law adopted in 1997.
Shults et al. (2001) [9] "Reviews of Evidence Regarding Interventions to Reduce Alcohol-Impaired Driving"	Median 7% reduction in measures of alcohol-related fatal crashes associated with 0.08 BAC laws. CDC strongly recommends all states adopt 0.08 BAC laws.
Dee (2001) [27] "Does Setting Limits Save Lives? The Case of 0.08 BAC Laws"	Statistically significant 7.2% reduction in the traffic fatality rate associated with the adoption of 0.08 laws in 14 states.
Eisenberg (2001) [28] "Evaluating the Effectiveness of a 0.08% BAC Limit and Other Policies Related to Drunk Driving."	Statistically significant reduction of 2.6% in the fatal crash rate associated with 0.08 BAC laws in 14 states.

Table 1 (*continued*) Studies of the effects of lowering the illegal BAC limit from 0.10 to 0.08 g/dL in the United States

Study	Results
Bernat et al. (2004) [19] "Effects of Lowering the Legal BAC to 0.08 on Single-Vehicle-Nighttime Fatal Traffic Crashes in 19 Jurisdictions"	Statistically significant reduction of 5.2% in SVN fatal crashes associated with 0.08 law across all states.
Tippetts et al. (2005) [18] "A Meta-Analysis of 0.08 BAC Laws in 19 Jurisdictions in the United States"	Statistically significant decline of 14.8% in the rate of drinking drivers in fatal crashes after the 0.08 laws were adopted in the 19 jurisdictions.
Gorman et al. (2006) [30] "Evaluation of the Texas 0.08 BAC Law"	Time series ARIMA analyses of fatal and non-fatal crashes revealed no effects due to the 0.08 BAC law.
Wagenaar et al. (2007) [17] "Effects of Legal BAC Limits on Fatal Crash Involvement: Analyses of 28 States from 1976 through 2002"	Pooled analyses resulted in significant decreases in SVN fatal crashes and in crashes involving drivers at low BACs (0.01–0.07 g/dL), medium BACs (0.08–0.14 g/dL), and high BACs (.15+ g/dL). The 0.08 law prevented an estimated 360 deaths per year and if the BAC limit was lowered to 0.05, an additional 538 lives could be saved each year in the United States.

A summary of the evidence for lowering the BAC limit to 0.05 g/dL or less

Effectiveness of 0.05 BAC laws

Several countries have conducted evaluations of lowering their illegal BAC limits to 0.05 g/dL or less. A multi-year study of the 0.05 g/dL BAC law in the Netherlands (adopted in 1974) concluded that it contributed to a sustained decline in the total number of drinking drivers involved in crashes [33]. A study from France evaluated the impact of lowering its BAC limit from 0.08 to 0.05 g/dL in 1996. Annual alcohol-related crash fatalities declined from approximately 100 before the legal change to 64 in 1997 in the province of Haute-Savoie, where the study was conducted [34].

In 1988, the illegal BAC limit was lowered from 0.08 to 0.05 g/dL in Austria. A study of the law found that there was an overall 9.4% decrease in alcohol-related crashes relative to the total number of crashes [35]. However, they noted that intense media and enforcement campaigns also occurred around the time that the limit was

lowered, making it nearly impossible to attribute the reductions to any one of these factors, at least in the short term. Bartl and Esberger [35] concluded that "lowering the [il]legal BAC limit from 0.08 to 0.05 g/dL in combination with intensive police enforcement and reporting in the media leads to a positive short-term effect." This provided support for the view that a 0.05 g/dL BAC illegal limit, as part of a comprehensive approach to fighting impaired driving, can have beneficial effects.

Homel [36] found that lowering the BAC limit from 0.08 to 0.05 g/dL in New South Wales, Australia, significantly reduced fatal crashes on Saturdays by 13%. Henstridge, Homel, and Mackay [37] conducted a rigorous time-series analysis of random breath testing (RBT) and 0.05 BAC laws in Australia, controlling for many factors including seasonal effects, weather, economic trends, road use, alcohol consumption, and day of the week. Although the primary focus of the Australian study was the impact of RBT, the findings on the effect of 0.05 BAC laws were also significant. The study statistically accounted for the effect of other alcohol countermeasures to determine the specific values of the declines that were attributable directly to either RBT or the lower 0.05 BAC limit. The study analyzed traffic data for periods ranging from 13 to 17 years and found that those Australian states lowering their BAC limits from 0.08 to 0.05 g/dL experienced meaningful declines in alcohol-related crash measures. After Queensland, Australia, reduced their *per se* BAC limit to 0.05 g/dL in 1982, they experienced an 18% reduction in fatal collisions and a 14% reduction in serious collisions. These results were not confounded by the effects of RBT, as it was not introduced until eight years later. Similarly, the 0.05 g/dL BAC limit in New South Wales was estimated to have reduced serious collisions by 7%, fatal collisions by 8%, and SVN collisions by 11%. This translated into the averting of an estimated 605 serious, 75 fatal, and 296 SVN collisions per year. Although the 0.05 g/dL BAC limit was introduced only two years before RBT in New South Wales, the authors accounted for this in their analyses and attempted to determine the crash reductions specifically attributable to each of the interventions.

Smith [38] specifically evaluated the effects of lowering the BAC limit in Queensland from 0.08 to 0.05 g/dL BAC. The proxy measure of changes in nighttime crashes as compared to daytime crashes was used. There was a significant 8.2% reduction in nighttime serious injury crashes (requiring hospitalization) and a 5.5% reduction in nighttime property damage crashes associated with the 0.05 g/dL BAC limit in the first year. Smith partially attributes some of the crash reductions in the second and third years after the adoption of 0.05 g/dL BAC to increased enforcement. When lowering the illegal BAC limit stimulates increased enforcement, it should be considered a benefit of the law, not a drawback, as concluded by Smith.

In South Australia, the illegal BAC limit was not lowered to 0.05 g/dL until 1991. Kloeden and McLean [39] reported that the number of nighttime drivers who had been drinking was reduced by 14.1% following adoption of the law. A second study of South Australia found that the 0.05 g/dL BAC limit did not significantly affect the number of fatally injured drivers who were legally impaired [40]. However, it did find that the proportion of impaired drivers at BACs of 0.15 or greater declined

from 1991 to 1993. This last finding supports other Australian research indicating that the lower BAC limit has a substantial effect on drivers with BACs higher than 0.15 [41]. It has been estimated that drivers with BACs higher than 0.15 are 244 times more likely to be involved in a fatal crash than drivers with 0.00 BACs [42]. The study by Zador et al. [4] found that male drivers aged 21 to 34 with BACs of 0.15 or higher are 573 times more likely to be killed in a single-vehicle crash than sober drivers of the same age. Thus, even though a 0.05 g/dL BAC limit would appear to be aimed at drivers with moderate BACs, its potential effect on the behavior of high-BAC drivers has important traffic safety implications.

Deshapriya and Iwase [43] determined that the 0.05 g/dL BAC limit adopted in Japan in 1970 had a substantial effect on drunk driving fatalities, nonfatal alcohol-related crashes and driving while intoxicated in Japan using multi-year trend analyses of crash and survey data. Bernhoft and Behrensdorff [44] found an increase in the proportion of drivers who reported that they would have no alcohol or restrict themselves to one drink within two hours in the first year after Denmark lowered their BAC limit to 0.05 g/dL BAC (from 71 to 80 %). However, they did not find a decrease in alcohol-related crashes in the first year after the law was adopted.

Sweden's more recent lowering of its limit to 0.02 g/dL BAC also showed positive results. Although Sweden adopted a 0.05 g/dL BAC limit in the 1950s, the move to an even lower limit in 1990 further improved traffic safety. Norström and Laurell [45] reported that in the six years following the introduction of the 0.02 g/dL BAC limit, there was a 9.7 % reduction in fatal crashes, an 11 % reduction in single-vehicle crashes, and a 7.5 % reduction in all crashes. Norström and Laurell noted that the most significant effects occurred in fatal and single-vehicle crashes, the two categories in which alcohol is most likely to be involved. This suggests that crash reductions cannot be attributed solely to existing trends but were caused, in part, by the lower BAC limit. These results were supported by another study in Sweden that estimated that the 0.02 g/dL BAC limit resulted in an approximate 10 % decrease in fatal crashes and a 12 % decrease in severe personal injury crashes [46].

Ediriweera, Shimizu, Pike, and Smith [47] reported that since the introduction of the 0.03 g/dL BAC law in Japan in 2002, statistically significant reductions in alcohol-related crashes, injuries and single vehicle nighttime crashes have been experienced by 16–19 year old drivers. Nagata, Setoguchi, Hemenway, and Perry [48] reported that the proportion of fatal crashes involving alcohol decreased from 15 % before to 11 % after the BAC limit was lowered from 0.05 to 0.03 g/dL BAC in 2002.

Table 2 summarizes the research on lowering the BAC limit to .05 g/dL.Table 3 summarizes the research on lowering the BAC limit to 0.03 or 0.02 g/dL BAC.

Impairment and crash risk at 0.05 g/dL BAC

Howat, Sleet, and Smith [49] conducted a review of the literature from experimental and laboratory research on the impairment effects at 0.05 g/dL BAC. Many

Table 2 Studies of the effects of lowering the illegal BAC limit to 0.05 g/dL in various countries

Study	Results
Noordzij (1994) [33] "Decline in Drinking and Driving in the Netherlands"	Percentage of drivers with BACs >0.05 g/dL from roadside surveys decreased from more than 15% in the years before the 0.05 limit to 2% in the first year and then leveled off at 12% for 10 years after the law change.
Mercier-Guyon (1998) [34] "Lowering the BAC Limit to 0.05: Results of the French Experience"	Alcohol-related traffic crash fatalities decreased from 100 before the limit to 64 in 1997, after the law change in the French Province where the study was conducted.
Bartl and Esberger (2000) [35] "Effects of Lowering the Legal BAC Limit in Austria"	Found 9.4% decrease in alcohol-related crashes. "Lowering the legal BAC-limit from 0.08% to 0.05% in combination with intense police enforcement and reporting in the media leads to a positive short-term effect."
Henstridge et al. (1995) [37] "The Long-Term Effects of Random Breath Testing in Adelaide"	Queensland (Australia) experienced an 18% reduction in fatal crashes and a 14% reduction in serious crashes associated with lowering the BAC limit to 0.05 g/dL. These results were not confounded with the effects of random breath testing. New South Wales showed an 8% reduction in fatal cases, a 7% reduction in serious crashes, and an 11% reduction in SVN crashes associated with lowering the BAC limit to 0.05 g/dL.
Smith (1988) [38] "Effect on Traffic Safety of Introducing a 0.05% Blood Alcohol Level in Queensland, Australia"	Significant 8.2% reduction in nighttime serious injury crashes and a 5.5% reduction in nighttime property damage crashes associated with lowering the limit from 0.08 to 0.05 g/dL. Partly the result of increased enforcement.
Deshapiya and Iwase (1998) [43] "Impact of the 1970 Legal BAC 0.05 mg% Limit Legislation on Drunk-Driver-Involved Traffic Fatalities, Accidents, and DWI in Japan"	Trend analyses indicate that the 0.05 BAC law has reduced both alcohol-related traffic crashes and DWI drivers in Japan.
Bernhoft and Behrensdorff (2003) [44] "Effect of lowering the alcohol limit in Denmark"	When the BAC limit was lowered from 0.08 to 0.05 g/dL in 1998 in Denmark, there was a significant increase in the proportion of drivers who reported that they would not drink at all or would have only one drink if they were driving (71% before to 80% after).

Table 3 Studies of the effects of lowering the illegal BAC limit to 0.03 or 0.02 g/dL

Study	Results
Norström and Laurell (1997) [45] "Effects of Lowering the Legal BAC Limit in Sweden"	Reported that in the six years following the introduction of the 0.02 g/dL BAC limit there was a 9.7% reduction in fatal crashes, an 11% reduction in single-vehicle crashes, and a 7.5% reduction in all crashes.
Borschos (2000) [46] "An Evaluation of the Swedish Drunken Driving Legislation Implemented on February 1, 1994"	Estimated that the 0.02 g/dL BAC limit resulted in an approximate 10% decrease in fatal crashes and a 12% decrease in severe personal injury crashes
Ediriweera, Shimizu, Pike, and Smith (2006) [47] "Impact of Lowering the Legal BAC Limit to 0.03 on Teenage Drinking and Driving Crashes in Japan"	Since the introduction of the 0.03 BAC law in Japan in 2002, statistically significant reductions in alcohol-related crashes, injuries, and SVN crashes have been experienced among 16- to 19-year-old drivers
Nagata, Setoguchi, Hemenway, and Perry (2007) [48] "Effectiveness of a Law to Reduce Alcohol-Impaired Driving in Japan"	Reported that the proportion of fatal crashes involving alcohol decreased from 15% before to 11% after the BAC limit was lowered from 0.05 to 0.03 g/dL BAC in 2002.

of the studies reviewed showed statistically significant decrements in driving performance at a BAC of 0.05 g/dL or lower. The authors concluded that young and inexperienced drinkers appear to be at the greatest risk at 0.05 g/dL BAC. They recommended that setting a uniform 0.05 g/dL BAC statutory limit should be one measure in a comprehensive approach to reducing impaired driving including other legal, social, behavioral, and environmental strategies to deal with the problem. Ferrara et al. [1] concluded in a review of the research literature that driving performance changes initially begin with any departure from a 0.00 g/dL BAC.

Moskowitz and Fiorentino [2] reviewed 112 scientific articles regarding the effects of alcohol on driving-related skills published between 1981 and 1997. They concluded that, by the time subjects reach 0.05 g/dL BAC, the majority of experimental studies examined reported significant impairment. After testing 168 drivers, Moskowitz et al. [3] concluded that the majority of the driving population is impaired in at least some important measures at BACs as low as 0.02 g/dL BAC.

Recent epidemiological studies [4, 5, 6] of the relative risk of being involved in a crash at various positive BAC levels indicate that the risk of crashing is substantially higher at 0.05 g/dL BAC compared to drivers at 0.00 g/dL BAC. Zador et al. [4] estimated that the risk of being involved in a fatal crash for drivers at BACs as low as 0.02–0.04 g/dL is anywhere from two times to five times higher than for drivers with BACs = 0.00 g/dL, depending upon age and gender. That same study

concluded that the risk of being killed as a driver in a single-vehicle crash is six to 17 times greater for drivers at BACs between 0.05 and 0.07 g/dL compared to drivers at BACs of 0.00 g/dL, and that the risk of just being involved as a driver in a fatal crash at BACs between 0.05 and 0.07 g/dL is four to 10 times greater than for drivers at BACs = 0.00 g/dL. As mentioned earlier, Compton et al. [5] and Blomberg et al. [6] concluded that the risk of being involved in any crash of any severity (property damage, injury, or fatal) for drivers with BACs at 0.04 g/dL or higher was significant (18% higher than for drivers at 0.00 g/dL). Further, drivers with a BAC of 0.05 g/dL have a 38% higher risk of crashing than drivers with BACs = 0.00 g/dL. At 0.06 BAC, that risk is 63% higher, and at 0.07 g/dL BAC, the risk is 109% higher than for drivers with BACs = 0.00 g/dL.

Evidence for lowering BAC limits for youth

The United States has taken the lead in adopting lower BAC limits for underage youth, although other countries are beginning to follow suit (e.g. Canada and Australia). In 1984, the U.S. Congress adopted measures to sanction states that did not adopt 21 as their minimum legal drinking age. By 1988, all states had enacted such laws. Because it was illegal for those younger than 21 to drink any alcohol, it seemed logical that underage drivers should have no alcohol in their systems when they drove. In 1995, the U.S. Congress passed a law requiring states to adopt so-called zero-tolerance laws for drivers younger than 21. By 1998, all states had passed laws making it illegal for any driver younger than 21 to have a positive BAC. In some states, any BAC at 0.02 g/dL or higher is illegal for youth; in other states, the level is set at 0.01 g/dL BAC or higher; in the remaining states, any BAC higher than 0.00 g/dL is considered illegal for drivers younger than 21. These zero-tolerance laws for youth lowered the illegal BAC limits for that population and have proven to be effective in reducing the number of fatal crashes involving underage drinking drivers.

A study of zero-tolerance laws in Florida, Maine, Oregon, and Texas was conducted by Lacey, Jones, and Wiliszowski [50] under a NHTSA contract. Nighttime single-vehicle crashes were reduced by as much as 36% in Maine and 40% in Oregon, as little as 5% in Florida, and not at all in Texas for drivers subject to the new zero-tolerance laws. Maine and Oregon, which had more experience with the law and had higher levels of enforcement and publicity, had the higher levels of effectiveness, as would be expected.

The Maryland 0.02 g/dL BAC law for drivers younger than 21 was evaluated under a NHTSA sponsorship with the primary objective of determining the effects of the law on crashes. The law went into effect on January 1, 1989. The number of drivers younger than 21 who were involved in crashes and "had been drinking" was collected from 1985 through 1990. An 11% decrease was found comparing the before-and-after crash data associated with the zero-tolerance law. Further, this 11% reduction was in addition to a general reduction in alcohol-involved crashes

and a reduction in all crashes (alcohol and nonalcohol) involving drivers younger than 21 [51].

Hingson, Howland, Heeren, and Winter [52] compared four states that passed zero-tolerance laws before 1989 (Maine, New Mexico, North Carolina, and Wisconsin) with four adjacent states that had no such law (Massachusetts, Arizona, Virginia, and Minnesota). Equal numbers of pre- and post-law years were examined in each of the four pairs of states monitoring nighttime fatal crashes involving teenage drivers in the age groups targeted by the law. Study states set different ages for the BAC law: New Mexico and North Carolina, younger than 18; Wisconsin, younger than 19; and Maine, younger than 20. As a group, the states that lowered their BAC levels for youth had significantly greater post-law reductions in nighttime fatal crashes among adolescents relative to adults (34% teens *vs*. 7% adults) than the comparison states (26% teens *vs*. 9% adults).

In a follow-up study, Hingson, Heeren, and Winter [53] compared 12 states (North Carolina, Wisconsin, Oregon, Arizona, Maine, Maryland, Ohio, Vermont, New Mexico, California, Rhode Island, and Georgia) that lowered illegal BACs for youth before 1991 with 12 comparison states (Virginia, Minnesota, Washington, Utah, Massachusetts, Pennsylvania, Indiana, New Hampshire, Colorado, Texas, Connecticut, and Alabama). During the post-law period, the proportion of fatal crashes that involved single vehicles at night declined 16% among young drivers targeted by those laws, while it rose 1% among drivers the same age in comparison states where BAC limits were not changed. Adult crashes declined only 5% and 6% in the two groups during the post-law period. The study found that significant declines in the proportion of nighttime single-vehicle crashes among young drivers occurred only in states that lowered the underage BAC limit to 0.02 g/dL or lower. In other states that reduced the young driver BAC limit to 0.04, 0.05, or 0.06 g/dL, there was no significant difference from states that did not lower the limit at all. (Note: All states in the United States have subsequently lowered their limits to 0.02 g/dL or lower.) The decline was only noticed for states that dropped the BAC level to 0.00 or 0.02 g/dL, true zero-tolerance laws rather than the mixed-message laws for youth (i.e., the 0.04 to 0.06 laws).

Zwerling and Jones [54] conducted a systematic review of zero-tolerance laws and their effect on alcohol-related injuries and fatalities. Six studies met their strict selection criteria. All six studies showed reductions in injuries and fatalities associated with the implementation of zero-tolerance laws, and in three studies, the reductions were statistically significant. The greatest reduction (22%) was reported in one study for SVN fatal crashes involving underage drivers in those states adopting zero-tolerance laws. Despite some methodological difficulties cited by the authors, the six studies presented "accumulating evidence in support of the effectiveness of these laws." The total evidence is strengthened even more because similar results were found in different countries (Australia and the United States) using different methods and different outcome measures. Wagenaar, O'Malley, and LaFond [55] found that the frequency of self-reported driving after drinking declined 19% and driving after binge drinking (5+drinks in one setting) declined 23% after lower limits were adopted for youth in 30 states in the United States.

Table 4 Studies of the effectiveness of lowering the BAC limit for youth

Study	Results
Blomberg (1992) [51] "Lower BAC Limits for Youth: Evaluation of the Maryland 0.02 Law"	A significant 11 % decrease in police-reported alcohol crashes involving drivers younger than 21 associated with the 0.02 law. Decrease was 50 % in six communities that highly publicized the law and enforcement of the law.
Hingson et al. (1992) [52] "Reduced BAC Limits for Young People (Impact on Night Fatal Crashes)"	As a group, states that lowered BAC limits for youth had significantly greater post-law reductions in nighttime fatal crashes among drivers younger than 21 relative to drivers older than 21 (34 % for teens; 7 % for adults) than the comparison states that did not lower the limit (26 % for teens; 9 % for adults).
Hingson et al. (1994) [53] "Lower Legal Blood Alcohol Limits for Young Drivers"	SVN fatal crashes declined 16 % in 12 states that lowered the limit for youth while it rose 1 % in 12 comparison states that did not lower the limit for youth. Adult nighttime fatal crashes declined 5 and 6 %, respectively, in the two groups.
Zwerling and Jones (1999) [54] "Evaluation of the Effectiveness of Low BAC Laws for Younger Drivers"	A systematic review of the effects of zero-tolerance laws indicate that all six studies showed significant reductions in injuries or fatalities associated with the implementation of lower BAC limits for youths aged 20 and younger.
Wagenaar et al. (2001) [55] "Lowered Legal Blood Alcohol Limits for Young Drivers: Effects on Drinking, Driving, and Driving-After-Drinking Behaviors in 30 States"	Frequency of driving after drinking and driving after five or more drinks declined 19 and 23 %, respectively. Lower BAC limits did not affect overall self-reported amount of drinking or vehicle miles driven.
Voas et al. (2003) [56] "Assessing the Effectiveness of Minimum Legal Drinking Age and Zero Tolerance Laws in the U.S."	Lower limits for youth have resulted in an average 24.4 % reduction in alcohol-positive drivers younger than 21 involved in fatal crashes since their implementation in the United States.

Voas, Tippetts, and Fell [56] analyzed data on all drivers younger than 21 involved in fatal crashes in the United States from 1982 through 1997. Quarterly ratios of BAC-positive to BAC-negative drivers in each of the 50 states were analyzed in a pooled cross-sectional time-series approach. After accounting for differences among the 50 states in various background factors, changes in economic and demographic factors within states over time, and the effects of other related laws (including safety belt usage laws), results indicated a significant 24.4 % reduction in alcohol-positive drivers younger than 21 who were involved in fatal crashes as-

sociated with the zero-tolerance laws. The policy in the United States of making it illegal for underage drivers to have any alcohol in their systems appears to have been effective in reducing the proportion of fatal crashes involving youthful drinking drivers.

Before the adoption of zero-tolerance laws, young drivers were under the same BAC limit standards as adults. Adopting zero-tolerance laws is the same as lowering the BAC limit from 0.10 (or 0.08) to 0.02 g/dL for drivers younger than 21. Young drivers perceive this change the same way that adults perceive lowering the limit to 0.08 g/dL or to 0.05 g/dL BAC – that the state or country is getting tougher on impaired driving.

Table 4 summarizes the research on lowering the BAC limit for youth.

Lower BAC limits for other populations

Jones and Rodriguez-Iglesias [57] evaluated the effectiveness of a law in the state of Maine in the United States that made it illegal for any driver convicted of DWI to drive with any alcohol in their blood system. The impact evaluation showed that in Maine, the percentage of DWI convicted drivers (repeat offenders) in fatal crashes decreased by 45 % (from 12.9 % to 7.1 %) after the law was adopted while that percentage increased in two comparison states.

Sun, Kahn, and Swan [58] compared injury crashes of motorcycle riders to those of passenger car drivers. About the same proportion of each group had measurable BACs, but the mean BAC of the positives was 0.124 g/dL for the motorcycle riders compared to 0.180 g/dL for the passenger car drivers. This and other evidence persuaded the authors to suggest that motorcyclists need lower illegal BAC limits for riding a two-wheeled vehicle. They concluded that there is a need for greater coordination and balance when operating a motorcycle as opposed to a four-wheeled passenger car.

Public support for lower BAC limits

Surveys in the United States indicate that most people believe they should not drive after two or three drinks [59]. This is equivalent to a BAC of 0.05 g/dL for many people [60]. Considering this reported attitude, the public (at least in the United States) favors a BAC limit of 0.05 g/dL. The countries that have already adopted 0.05 g/dL BAC (or lower) as their limit usually report general support for the law (e.g., Australia, France, and Germany).

Conclusion

Mann, Macdonald, Stoduto, Bondy, and Shaikh [61] reviewed all of the available scientific evidence in assessing the potential impact of lowering the BAC limit to 0.05 g/dL. They assessed research on the effects of alcohol on driving performance; epidemiological research on the risk of collision involvement at various BACs; research on the impact of lowering the BAC limit in other countries and jurisdictions; and other possible issues such as public acceptance, police discretion, and judicial outcomes. This review concluded that the adoption of a 0.05 g/dL BAC could potentially reduce the motor vehicle crash fatalities by 6 to 18 % in Canada. In a subsequent international review, Mann, Macdonald, Stoduto, Bondy, Jonah and Shaikh [62] concluded that most, but not all, studies showed beneficial effects on traffic safety measures due to lowered BAC limits. They suggest that most of the effects of such laws are due to general deterrence.

Chamberlain and Solomon [7] conducted an extensive review of all of the issues surrounding a 0.05 g/dL BAC limit. The review summarized the effects of low doses of alcohol on driving behavior, the relative risk of a crash at various BAC levels, and the experience in other countries with lowering BAC limits, and presented a compelling case for a 0.05 g/dL BAC limit around the world.

The scientific evidence accumulated over the past 50 years indicates a direct relationship between rising BAC levels and the risk of being involved in a motor-vehicle crash and documents that driving performance begins to deteriorate significantly at 0.04–0.05 g/dL BAC [63, 64, 65]. Because alcohol has been shown to have a wide variety of effects from subject to subject, special attention needs to be given to the selection of a BAC level in which the vast majority of drinking drivers are likely to be affected. This level appears to be 0.05 g/dL BAC. When all of the international evidence on lowering BAC limits is assembled, reviewed, and summarized, it is concluded that lowering the illegal BAC limit to 0.05 g/dL (or lower for countries that have had 0.05 g/dL limits for several years) is an effective strategy in reducing impaired driving.

In general, the literature reveals that lowering the BAC illegal limit reduces drinking driver fatal crashes, whether it is from 0.10 BAC to 0.08 g/dL or from 0.08 to 0.05 g/dL or from 0.05 to 0.03 or 0.02 g/dL for adults, or from some higher BAC level to 0.02 g/dL (or lower) for youth. The general public does not think people should drive after two or three alcoholic drinks. This translates to 0.04 or 0.05 g/dL BAC for most people. Laboratory research shows that most people's critical driving skills are significantly impaired at 0.04–0.05 g/dL BAC. The World Health Organization [66] recommends an upper limit of 0.05 g/dL BAC for the general driving population and 0.02 g/dL BAC for young drivers as the best practice at this time.

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Interventions to reduce impaired driving and traffic injury

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Abstract

This review characterizes the effectiveness of various interventions to prevent impaired driving and reduce traffic injury and death. Interventions are considered within the ecological/health promotion framework, and include: 1) economic interventions, 2) organizational interventions, 3) policy interventions, and 4) health education interventions, including the use of media, school and community education and public awareness programs. Alcohol or drug-impaired driving arises from complex and multiple and interrelated causes. Therefore, prevention efforts will benefit from approaches that rely on a combination of interventions, including educational, behavioral, environmental, and policy approaches. Effective approaches strengthen the skills and capabilities of individuals to take action and the capacity of groups or communities to act collectively to exert control over the determinants of impaired driving. There is strong evidence for the effectiveness of some interventions, including economic and retailer interventions, alcohol taxation, reducing alcohol availability, legal and legislative strategies, and strategies addressing the servers of alcohol, such as server liability and server intervention. There is also evidence for the effectiveness of sobriety checkpoints, lower BAC laws, minimum legal drinking age laws, and supportive media promotion programs. Other interventions with moderate evidence of effectiveness include restricting alcohol advertising and promotion, community mobilization efforts, and ignition interlocks in vehicles of convicted drink-drive offenders. Health education by itself has insufficient evidence for effectiveness, as is also the case with passive server training programs, school drug and alcohol education programs, and health and safety warnings. Taken together, educational, behavioral, environmental and policy approaches to reducing impaired driving using all four components of the ecological/health promotion model are likely to be the most effective.

Introduction

Since the advent of the motor vehicle, alcohol and drugs have been among the most significant risks for traffic injuries. Despite the scope of the drug and alcohol problems globally, and the difficulty in preventing them, there is increasing evidence of the effectiveness of some prevention strategies, especially those aimed at reducing alcohol-impaired driving and its effects on traffic injuries [1]. Over the past three decades, high-income countries have experienced a substantial reduction in mortality and morbidity from alcohol-related traffic crashes [2]. The majority of this reduction is attributed to behavioral changes associated with legislation, public education, organizational policies, law enforcement, and economic incentives and disincentives, in multiple settings involving multiple sectors [3, 4].

This chapter adopts an ecological and health promotion framework to review evidence regarding the effectiveness of these and other interventions to reduce alcohol and drug-related traffic injuries,[1, 5]. Ecological approaches are grounded in the notion that health has multiple causes and stems from a reciprocal relationship between a person and their environment (i.e. behavior is viewed as being affected by, and affecting the environment). Health promotion is concerned with improving health-related behaviors of populations.

Evidence is primarily drawn from interventions in high income countries, and the discussion focuses on the potential benefits of synergistic application of these interventions. There is a paucity of literature on the effectiveness of interventions to reduce impaired-driving and traffic injuries in low income countries, and while these countries can learn much from experiences in high-income countries, extrapolation to dissimilar settings should be done cautiously.

Ecological/health promotion approach

Drinking and driving behavior is not only shaped by individual choices and motivation, but also strongly associated with organizational, economic, environmental, and social factors. As a result, approaches attempting to bring about change in drinking and driving behavior through education alone are likely to have limited or no success [2, 6]. Those that combine educational with other behavioral, environmental, policy and organizational changes are more likely to have impact [7–9]. Because alcohol consumption is a necessary condition for alcohol-impaired driving, social-environmental factors that influence alcohol use should be considered when designing a comprehensive prevention strategy. Examples of such factors include alcohol use by family members and peers, images of alcohol use promulgated by advertising and media, and the availability and cost of alcoholic beverages [10–12].

An ecological/health promotion approach to the prevention of alcohol-related traffic injury incorporates an appropriate balance of individually-focused behavior change strategies and those that encourage supportive environments and conditions of living conducive to health. Health promotion involves any combination of

educational, organizational, economic and political actions designed to enable individuals, groups and communities to control and improve health through changes in knowledge, attitudes, behavior, policy, and social and environmental conditions [13]. Ecological/health promotion approaches focus on building health public policy, creating supportive environments, strengthening community action and changing personal health behaviors.

Ecological/health promotion approaches to impaired driving requires a broad range of individual and community actions, fostered by education, stimulated by social norms, and encouraged through healthy public policy [14, 6]. These efforts require strong community support to achieve legislative change, and legislative change is critical for shaping personal behavior and social expectations [15–17]. Four general classes of intervention approaches have been identified using the ecological/health framework[18]:

– Economic interventions
– Organizational interventions
– Policy interventions, and
– Health education, school and community interventions.

Within each category there is a wide variety of strategies that could be employed to reduce impaired driving related traffic injuries. An example of how this approach could be applied to the problem of impaired driving is provided in Figure 1.

We briefly review these strategies embedded within the components of the framework, and identify which have strong evidence of effectiveness and where

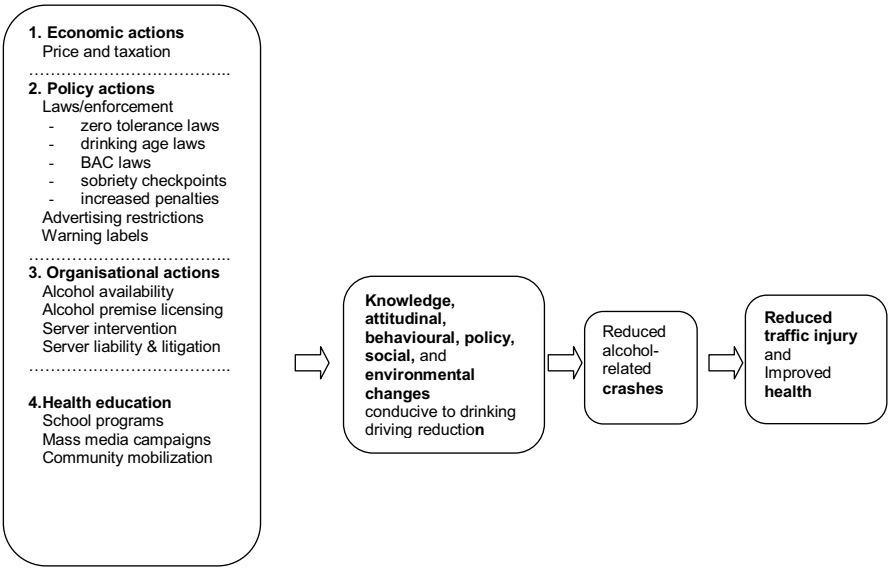

Figure 1 An ecological/health promotion framework for reducing impaired driving and related traffic injury.

there is equivocal or insufficient evidence. Because so little is known about intervening to prevent drug-related traffic injuries, only a small discussion of what is known is presented. Most of the examples will focus on reducing alcohol-impaired driving and traffic injuries.

Economic interventions

Pricing policies are regarded as among the most effective measures to reduce total alcohol consumption and hence alcohol-related problems. Studies have indicated that a rise in price will lead to a drop in consumption [8, 12, 19] and a decrease in price will likely result in additional alcohol-related deaths [20]. One estimate indicated that a 10% increase in the price of alcoholic beverages in the United States would reduce alcohol-impaired driving by about 8% for females and about 7% for males [12]. Another estimate shows that a 17% increase ($1) in the price of alcohol for a six-pack of beer could lead to a 3.3% reduction of current alcohol-attributable mortality in the USA [21]. Pricing policies are likely to be especially effective in reducing consumption by young people, since their disposable income is generally low. Moreover, an increase in the real price of alcohol has been shown to significantly reduce alcohol-attributable harms among indigenous peoples for whom high levels of overall alcohol consumption and alcohol-impaired driving are of particular concern [22]. In both Australia and the United States, there is widespread support for alcoholic beverages to be taxed based on their alcohol content, and for tax rates to be periodically adjusted to reflect changes in real costs to the consumer [23, 24].

Organizational interventions

Alcohol licensing

The licensing of sellers of alcoholic beverages is crucial for the adoption of many organizational interventions. Thus, it is a central component of effective prevention. The power to revoke or suspend a license for breaches of sales regulations is an effective strategy for reducing the rates of alcohol-related problems, including traffic crashes [12].

Alcohol availability

There is substantial evidence that alcohol availability is correlated with levels of consumption and ultimate harm [8, 25, 26]. Availability of alcohol can be controlled by restrictions on hours and days of sales, and by controlling the number, location,

and type of liquor outlets. There is strong evidence that off-premise monopoly systems can limit both the levels of alcohol consumption and of alcohol-related problems such as drink driving [27].

Eight studies of privatization in the U.S., Canada, and Scandinavia showed that privatization of alcohol sales were associated with increased alcohol consumption and related harms. Examples from Finland and Sweden illustrate substantial rises in consumption, including by minors, associated with availability of alcohol in grocery stores [12]. When Swedish grocery stores were no longer permitted to sell 4.5% beer, a significant drop in traffic crashes followed [12]. One study of government re-monopolization indicated that re-monopolization back to the government may reduce these harms [27]. There is inconsistent evidence on the effectiveness of changing hours of sale of alcohol.

Alcohol bans

Total bans have been effective in isolated environments without other sources of alcohol. This finding is based on seven studies of bans and lifting of bans, mainly among American Indian, Alaska Native, and Inuit communities in Canada [27], in specific groups (e.g. minors) or in specific circumstances (e.g. during sporting events) [28, 29].

Reducing alcohol outlet density

Alcohol availability in neighborhoods with a high density of outlet stores has been associated with alcohol-related problems [30]. When governments relinquish monopoly control over the retail sales of alcoholic beverages, outlet density increases. While no studies looked at the effects of local intervention to limit outlet density, several types of studies consistently indicated that outlet density and policy changes that affect density were associated with excessive alcohol consumption and related harms [27]. Alcoholic beverage retail privatization, when governments relinquish monopoly control over the retail sales of alcoholic beverages, commonly results in increased alcohol outlet density, among other changes [27].

Server intervention and drinking environments

Increasing attention is being paid to issues of server training and the safety of drinking environments in the United States, Australia, Sweden and Canada [7, 12, 31, 32]. Server intervention programs involve training staff employed to serve alcohol beverages in alcohol retail establishments. Their main objective is to prevent intoxication and drink driving by their clients. Recommended serving practices include providing food, slowing service to drinkers showing signs of intoxication, refusing

service to intoxicated or underage drinkers, and taking steps to prevent intoxicated patrons from driving. Reviews of server intervention found evidence of effectiveness, under conditions of face-to-face instruction and strong management support [7] and with mandatory regulations and meaningful enforcement [33].

The introduction of voluntary "Alcohol Accords" (or codes of practice agreed on between local alcohol retailers, police, local government and community groups) is one method to promote responsible service policies. Despite a number of Alcohol Accords in place throughout Australia, the evidence of their effectiveness is equivocal [31]. One program – the Alcohol Linking Project in New South Wales, Australia – was successful. Police fed information on the location of drinking drivers' last place of drink back to the drinking establishment and audited the worst 8% of premises to ensure they were complying with the Liquor Act. For premises that received letters and visits, alcohol-related incidents reported by police dropped 36%, compared to a 21% drop in control premises. In a subsequent evaluation there was a 13% drop in incidents linked to premises that received targeting enforcement policing, with a 32% drop in major motor vehicle crashes [34].

Server liability

In Australia, alcohol-consuming patrons involved in subsequent crashes have successfully sued bar and hotel proprietors following traffic crashes by claiming they were served dangerous levels of alcohol [35]. Similarly, studies from the United States have found that alcohol-related crashes decreased following high-profile server liability cases [36], and that states with statutes or case law permitting server liability tend to have lower fatality rates from alcohol-related crashes [37, 38].

Policy interventions

McGinnis et al. [39] argue strongly for the central role of policy development in promoting health. The enactment of laws, along with enforcement and informational efforts, have resulted in substantial declines in the rate of alcohol-related traffic crashes in countries such as the United States, Australia and New Zealand [40, 41, 42].

Breath alcohol ignition interlocks

Breath alcohol ignition interlock systems are used in some countries to discourage drinkers from driving, and have shown effectiveness in reducing impaired-driving arrests while on the vehicles of convicted drunk driving offenders [43, 44]. The system is designed to detect the presence of alcohol in a driver's breath by requiring the driver to blow into a device that measures the breath alcohol concentration.

If the device registers a threshold amount of alcohol, the ignition of the car will not start. The benefits of interlocks are only sustained while they are installed in a vehicle. Alternative alcohol measurement technologies may improve their use as a deterrent among the general public in the future.

BAC limits

Many countries have laws, known as illegal "*per se"* laws that specify BAC limits at which it is illegal to operate motor vehicles. Recent literature reviews indicate that lowering the "*per se*" limit to 0.08 g/dL or lower has been effective for decreasing alcohol-related crashes in the United States [7] and internationally [45]. In the United States, Congress required states to implement 0.08 BAC laws by October 2003 to avoid the withholding of federal highway construction funds [7]. In the early 1990s, Australia also used such "economic incentives" to encourage states to introduce a uniform BAC limit of 0.05% [41, 46, 47]. Lower BAC limits specifically for young or inexperienced drivers are also effective at decreasing alcohol-related crashes [7]. All 50 U.S. states have these laws, as does Australia, New Zealand, Austria and parts of Canada [7, 46].

Sobriety checkpoints

Sobriety checkpoints allow law enforcement officers to assess drivers for alcohol impairment. In Australia and a number of European countries, drivers are systematically stopped and given breath tests to measure their BACs. In the United States, police must suspect a driver has consumed alcohol before they can demand a breath test. Both of these breath test procedures are usually accompanied by extensive publicity in an attempt to alert drivers to the consequences of drink driving and to increase their perceived risk of arrest [7, 42]. Evaluations of the effects of sobriety checkpoints on crashes in the United States and Canada indicate that they decrease alcohol-related crashes by approximately 20% to 30% [7, 41, 42, 48]. The success of checkpoint programs is dependent on both the level of enforcement and on publicity campaigns. Economic assessments in the United States, Australia and the Netherlands indicate significant societal cost savings from sobriety checkpoint programs [7, 12].

Increased penalties for drink driving

Australian data indicates that harsh penalties for drink-drivers has the highest level of public support (89%) among the many policy-oriented interventions [49], yet there is little evidence of substantial benefits from increased fines or mandatory jail time [50]. In contrast, the bulk of the evidence indicates that administrative license

suspension or revocation appear to be effective interventions to achieve both specific and general deterrence [42].

Drinking age

A global review of alcohol policies [19] indicated a relationship between raising the drinking age and a reduction in alcohol consumption and alcohol-related problems among young people. There is strong evidence from the United States that increasing the drinking age to 21 years resulted in substantially fewer alcohol-related crashes among young people [7]. Similarly, alcohol-related problems in the United Kingdom decreased after the minimum age for drinking in public places was raised [8]. Conversely, there is evidence of an increase in hospitalized injuries associated with alcohol-related traffic crashes when the legal drinking age was lowered from 20 to 18 years in New Zealand [51].

Restrictions on advertising and promotion

Advertising and marketing strategies once used by the tobacco industry are also used to increase the market share of alcoholic beverages [52, 53]. The goal is to "normalize" regular drinking, and encourage drinkers to consume more [54, 19]. There is increasing evidence that advertising and promotion act as reinforcing factors for consumption [19], especially in youth [55], and there seems to be a link between advertising and increased consumption of alcohol by young people [56] who are old enough to drive. Hollingworth and colleagues [21] estimated that a complete ban on alcohol advertising could result in a 16.4% decrease in alcohol-related life-years lost in the USA. A partial ban could lead to a 4% reduction.

Regulations governing the promotion of alcohol have been relatively ineffective at reducing alcohol-related harms in Australia and the United States [54]. Voluntary codes of advertising have been adopted by the industry as part of a philosophy of self-regulation [57], but are considered generally ineffective [58]. To reduce drinking and driving, voluntary restrictions should be used only as part of a more comprehensive set of alcohol control policies [59].

Health and safety warnings

The warning that "consumption of alcoholic beverages impairs your ability to drive a car or operate machinery, and may cause health problems" is prominent among alcoholic beverage warning labels in many countries [12]. While a significant proportion of the population reports "noticing" the warning labels, different warning label designs can significantly reduce their effectiveness [60]. To date, the long-term effects of alcohol warning labels on drinking and driving behavior is unknown and their effectiveness is still unproven [19, 40, 61].

Multiple policies

The implementation of multiple policies to reduce alcohol-related harms is generally preferable to reliance on any single strategy because of the potential for synergistic effects [5, 13, 62]. An analysis of alcohol control policies in 97 American cities showed a relationship between the number of regulations and alcohol-related traffic fatalities. Cities with less than 10 of 20 listed alcohol control regulations had 1.46-times more deaths than cities with 15 or more of these regulations [63]. Australian research indicated substantial economic benefits from employing multiple interventions simultaneously (such as sobriety checkpoints, lower legal BAC limits, mass media publicity, higher penalties and stricter enforcement of penalties) [3]. Key to the success of drink driving policy interventions is a change in the public perception of the risk of being involved in a crash or of being arrested for drink driving, or both [19]. Increasing awareness and knowledge, and improving the acceptance of traffic regulations through the use of public media campaigns can make policy and legislation more acceptable to the public [11, 41, 47].

Health education, school and community interventions

Direct health education

Health education, health information, and health instruction aimed at altering driver behaviors has met with limited success. However, most interventions have been poorly designed (e.g. without any theoretical bases) and/or inadequately evaluated [64, 65]. The evidence suggests that for behavior change to be effective, a supportive environment (via organizational, economic and political actions) is usually necessary [15, 16, 66]. As a result, it is important that education programs also encourage community members to seek changes in policies and practices that help reduce alcohol-impaired driving. Specific education efforts also need to be directed at opinion leaders and policy makers, to support structural changes in the drinking and driving environment.

School programs

Evidence for the effectiveness of school-based alcohol interventions is unclear, and evaluations of drink-drive programs in schools are scarce. Many school programs have been short term and have operated in isolation from other alcohol control initiatives in the broader community [67]. Even among programs with sound research designs, their effects are often small [64, 68] School programs achieving positive outcomes have been thoroughly grounded in educational and behavioral change theory and used life skills training to target drinking behaviors of young people [69, 68]. One such program, The Northland Program [70] was successful in reducing

monthly drinking by 20% and weekly drinking by 30% in young adolescents. In addition to providing opportunities to engage students, the school setting may also be appropriate as a venue to engage parents in programs, but such approaches have not undergone sufficient empirical research to measure their effectiveness on drinking and driving.

Mass media campaigns

Mass media strategies have been used extensively to promote health-enhancing behaviors. There is evidence that well devised and adequately resourced mass media programs can improve health related behaviors [71, 72]. A systematic review by Elder et al. [73] found strong evidence that mass media campaigns against drinking and driving are effective in reducing alcohol-impaired driving and crashes when they are carefully planned, well-executed, attain adequate audience exposure, and are implemented in conjunction with other ongoing prevention activities, such as law enforcement. Such campaigns were found effective regardless of whether they focused on the law and enforcement or when they focused on the health and social consequences of drinking and driving. Mass media campaigns in isolation, however – from the limited evidence available – appear to have limited effectiveness in reducing or preventing alcohol-related problems [71, 32]. Nonetheless, mass media campaigns can play an important role in raising awareness about alcohol issues, generating public debate, reinforcing health related messages, and changing perceived norms.

Community mobilization

There is some evidence that community mobilization or community action projects involving local groups have been effective in reducing alcohol-related harm [74, 75]. In the US, a combination of community interventions resulted in a 42% reduction in fatal crashes involving alcohol [66], and a five-community comprehensive intervention significantly reduced alcohol availability and fatal traffic crashes [75] Mothers Against Drunk Driving (MADD) in the United States has been very effective in organizing community action for change in drunk driving [76]. Multicomponent interventions with community mobilization are recommended to reduce alcohol-impaired driving by the US Taskforce on Community Preventive Services (http://www.thecommunityguide.org).

Interventions related to drugs and driving

While there are some prescription medications that impair driving, this review will focus upon illicit drugs and driving. Given the illicit nature of the drug use, agencies are unable to use the full range of ecological interventions.

The focus of current practice is education and policy interventions. Compared to the science associated with the detection of alcohol at levels that impair driving, the science of detecting drugged driving is still in development. Nonetheless, several steps are being taken to address drug driving around the world, including changes to drug driving legislation, media campaigns warning of the dangers of drug driving [77, 74], training of drug recognition experts [79] and road side testing and supporting laboratory based blood testing [80, 81]. However, these steps are being taken in the face of continuing concerns over nearly every element of drug driving interventions.

The inconclusive data related to determining impairment at given dosages [82] and the sensitivity issues associated with the road-side testing and half-life of drugs [81] are perpetual challenges for the future. While Walsh et al. [83] provided a summary of risk associated with six major drug groups, and despite numerous studies around the world that identify drugged driver fatalities [84] there is still limited evidence regarding levels of impairment associated with specific consumption of illicit drugs (except cannabis), especially in non-laboratory settings. In particular, DUI legislation requiring the proof of driving impairment, measured as a person being "incapable of being in proper control of the vehicle", is difficult to prove without more sensitive metrics related to drug testing [85].

Furthermore, differing cultural beliefs associated with illegal drugs, issues related to poly drug use, the large number of illegal drugs accessible, unknown levels of the active ingredients in illegal drugs, and the burgeoning increase in fatal drug overdoses, limit what we can say definitively about interventions to prevent drug-related traffic injuries.

Recognising these limitations Western Australia modified their road traffic act to enable random drug testing for cannabis, methamphetamine and MDMA (Road Traffic Amendment Drug Driving Bill). The new legislation made it an offence to drive with any detectable presence of these drugs in oral fluid or blood. The legislation makes no attempt to quantify the level of impairment. If police suspect impairment they can follow standard assessment procedures requiring laboratory based blood and urine analysis. If confirmed, the driver can be charged with the higher offence "driving while impaired by a drug". Between October 2007 and April 2008, 4229 drivers were tested with 177 positive results; 114 drivers were charged with drug driving and 63 are still waiting on laboratory analysis [86].

Despite the paucity of intervention effectiveness data, theory-based models have been developed suggesting that many of the same strategies used to reduce alcohol-related traffic injuries and death may also apply to drug-impaired driving [87]. Special emphasis is given to the potential of changing public policy, such as:

Laws and Their Enforcement: laws to regulated or prohibit sale, manufacture, and use of substances along with the enforcement of these laws has been shown effective in reducing substance abuse.

Availability and Price: less availability and higher prices have been shown to decrease substance abuse.

Community Norms: permissive community norms that tolerate alcohol and drug abuse have been linked to increased substance abuse.

More efforts will be needed to explore effective policy interventions to reduce substance use beyond those related to basic interdiction efforts.

Discussion

This chapter has outlined the benefits of taking an ecological/health promotion approach to reducing alcohol and drug-related traffic injuries. These approaches are most likely to result in changes within the control of individuals (such as decision making) and those outside their direct control in the social, economic and environmental arenas (such as pricing, promotion, sales, availability, peer pressure, and alternative transportation) [88, 89]. According to this perspective, the most effective means of changing impaired driving behavior is through a combination of educational, organizational, economic and political actions [90]

Among the various applicable component strategies within the ecological/health promotion framework, the evidence of effectiveness varies from strong evidence for some policies to inadequate evidence for some education efforts directed at individuals. Effective component strategies include economic and retailer interventions, specifically those centering on taxation tied to alcohol content, reducing availability and server liability, sobriety checkpoints and random breath testing, lowering the legal BAC limit, minimum legal drinking age laws, supportive media promotions and other relevant governmental laws/regulations. Supporting the importance of taking a health promotion and ecological perspective, these interventions have had their greatest impact when administered in the context of other on-going drink driving interventions in the community.

For other component approaches, evidence of effectiveness is moderate, with evidence for some interventions either absent or inconclusive. Strategies such as those that restrict advertising and promotion which competes with the messages promulgated by the alcohol industry may, under some conditions, be influential in addressing alcohol impaired driving. Although there have been some positive outcomes from implementing interventions – such as server intervention, modifying physical drinking environments, conducting theory-based school drug and alcohol education programs, incorporating community mobilization initiatives, and college and worksite programs – the overall evidence supporting their individual efficacy is weak. There is no good efficacy data on the impact of interventions to reduce drugs and driving.

One of the limitations in this overview of specific strategies is that many of the interventions were implemented and evaluated without considering potential synergistic effects. The ecologic effects of implementing numerous interventions simultaneously is difficult to evaluate, but important to consider in any multi-level effort to apply the health promotion framework to alcohol-impaired driving.

A second limitation in this overview is that the impact of specific interventions was limited to research in high income countries, mainly Australia and the United States. Consequently, the generalizability of these effectiveness data to applications in low and middle income countries is uncertain. Any well-planned impaired driving strategy should be adapted for local conditions. The effectiveness of many of the interventions described here may depend on the economic infrastructure of a country or region, the political landscape, and the presence of a culture of safety

[91]. Hence, the transferability of these strategies to other settings needs further examination.

Levels of public support for policies, educational efforts and organizational actions to prevent alcohol-impaired driving often bear little relationship to the evidence for their effectiveness, but greatly influence decisions about which approaches to implement. Approaches with limited evidence of effectiveness on their own may nevertheless prove useful when embedded in a multi-faceted program, as the interventions with the strongest direct effects will drive change, and the weaker ones may reinforce and support change. Consequently, while advocating for strategies with demonstrated effectiveness, the field should also continue to support research on interventions that currently have only moderate or insufficient evidence to strengthen their evidence-base.

Educating and informing the public and policy-makers regarding the effectiveness of impaired driving prevention strategies, and the need for them, is an important aspect of public health and health promotion. Such efforts can help modify community attitudes and behaviors, and foster a receptive climate for policy and organizational change. One important resource to help communities achieve this goal is a drinking and driving road safety manual for decision makers [92].

Ecological/health promotion approaches require consideration of the many ways in which change in alcohol and drug-related harms can occur, and the many opportunities for leveraging community resources to reduce impaired driving and improve health. Using an ecological/health promotion approach to plan and implement comprehensive community-based drug and alcohol prevention programs that reduce traffic injuries offers our best hope for success.

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Disclaimer

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The alcohol ignition interlock and other technologies for the prediction and control of impaired drivers

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Abstract

This chapter summarizes the context and evidence supporting the use of alcohol ignition interlocks (also known as "alcolocks") as an approach to improving road safety. Interlocks usually have four features: (1) an in-vehicle sensor that requires a breath sample and prevents engine starts if alcohol level exceeds some criterion such as blood alcohol concentration (BAC) ≥0.02 g/dL; (2) a running retest feature which requires at least one retest after the car has been started, often every 15 to 45 minutes while driving; (3) a tamper-detecting installation in the engine compartment; and (4) a data-recording feature that logs the time and level of all BAC tests, starts, stops, and procedural violations. These devices form the base of an interlock program that, depending on the quality of the policies, reporting procedures, and user supports, can range from very weak to very effective. The USA through the National Highway Traffic Safety Administration, (NHTSA), Canada through Transport Canada, Australia through Standards Australia, and the European Commission through CENELEC[1] have promulgated standards and guidelines in an effort to make these devices and their programs maximally effective. This report provides some background and context for the development of interlock programs and then focuses on the evidence for interlock program effectiveness and promising aspects that are still under-exploited. Reports that have combined data from multiple studies estimate that interlocks account for 65 % reductions in driving while impaired DWI recidivism, a beneficial effect that is usually limited to the period of installation. Currently, there are still too few interlocks in service to substantially alter the rate of alcohol-impaired crashes. The attainment of ideal program features is a work in progress, and all developed nations that have taken an interest in interlocks are actively groping toward a set of best practices.

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[1] The 29-nation European Committee for Electrotechnical Standardization (CENELEC)

Background on the growth of ignition interlock programs

In the past 25 years, there has been a large reduction in the proportion of all roadway deaths that are caused by alcohol. This has been documented in most developed nations, and researchers understand these improvements to have been a consequence of better laws, better enforcement, and more public demand for safer roads throughout the industrialized world. Nonetheless, to the extent that data can be compared, in the majority of developed nations the percentage of roadway deaths that involve alcohol still ranges between 20 and 40% of all fatal crashes. In the USA, alcohol-impaired driving contributes to the death of approximately 17 000 people annually and, across the past several years, this represents a fairly stable rate of about 40% (± 1%) of all fatal crashes.

The alcohol ignition interlock is a DWI control device that, when installed in a car, will prevent its engine from starting until the driver blows into a sensor with a breath alcohol concentration less than a set level, usually in the range of 0.02 g/dL to 0.04 g/dL. Several evaluation studies have determined that ignition interlock programs lead to 40 to 90% reductions in DWI re-arrest while the devices are installed [1]. A meta-analysis that used Cochrane Collaboration rules for the selection of studies calculated a 64% reduction in recidivism among those who install interlocks [2]. The reduction is limited to the period when the interlock is installed, but this is nonetheless a significant safety benefit. However, those who install interlock devices do not necessarily represent the highest risk offenders, and one of the major challenges to interlock programs is to enroll a higher proportion of all DWI offenders. Some offenders defy court orders to install a device, or simply reject the opportunity provided by the licensing authority to drive safely and legally with an interlock; driving without a license is often elected as a more attractive choice since the risk of detection is so low.

It is common to distinguish between the device (the interlock) and the program (the laws, monitoring procedures, education, and in some cases medical services and counseling adjuncts associated with the interlock). Most agree that good programmatic support is a necessary element in the success of this approach. The first interlock program was begun as a pilot test in California in 1986; today, all but a few U.S. states and Canadian provinces have laws that support interlock programs, even if only weakly. In virtually all North American programs, interlocks are used with convicted DWI offenders.

Sweden has implemented a nationwide interlock program for offenders, as well as a pilot program of primary prevention interlocks for commercial fleets, such as taxis, buses, and trucks. The commercial program has been judged successful and is going to be required nationwide in 2009. In primary prevention programs, drivers will not have been selected for the interlock because of prior alcohol problems, but simply as a preventative. Several regions within the European Union and several Australian states have been evaluating interlock programs and some of these, similar to Sweden's, will be primary prevention programs. The UK recently conducted a pilot program to assess user acceptability. As part of a multinational feasibility

study in the European Union, Spain, Norway, and Germany installed interlocks in public buses, commercial trucks, and other safety sensitive vehicles [3, 4]. In addition to these commercial programs, Belgium has completed a small trial with alcohol offenders. Elsewhere in Europe, an offender pilot program that began as a local initiative in the Haute-Savoie region of France has been successfully implemented and is now undergoing trials in judicial courts beyond Annecy [5].

All of the nations with developing ignition interlock programs are affluent democracies where technology for road safety problems is routinely embraced. The costs of the interlock program for the offender are generally very low compared to the costs of alcohol. When interlocks are used following a DWI arrest, the cost of the interlock program is borne by the person convicted of DWI. In US dollars, the cost is about $2.20/day in addition to a one-time charge of approximately $125 to install the devices (less than $1000/year). In North America, Australia, and Western Europe, the economics of interlock programs make sense because the driver pays, and the daily cost of a lease fee is about the price of one alcohol drink per day. In some US States, such as New Mexico in the United States, everyone who installs an interlock pays a 10% fee that supports a fund used to offset the interlock costs for people with little money.

In Sweden, the cost of the interlock program at 50 000 SEK (5000 €; $7300) is considerably higher because the interlock program runs for two years and is embedded in a medical monitoring program that requires periodic blood samples for the estimation of alcohol biomarker levels. Nonetheless, a study reported by Bjerre, Marques, Selen and Thorrsen [6] demonstrated a reduction in the use of sick leave and hospital inpatient days for offenders who participated in the interlock program. In a follow-on study, Bjerre, Kostela, and Selén [7] calculated that health care costs were 25% lower for interlock program participants than for comparison subjects. Accordingly, this could be quite a good deal for the public since the offender pays the costs of the program and the larger society reaps both the cost and safety benefits. The strict abstinence-only program has a high attrition rate, however.

The use of interlocks for DWI offenders moved slowly from 1986 to 2005 even in jurisdictions that were otherwise interested in interlocks. In 2006, the pace of installation in the United States and Canada began to increase sharply following promotional efforts by the effective citizen action groups, Mothers Against Drunk Driving (MADD) USA and MADD Canada. MADD's newest Campaign to End Drunk Driving now features ignition interlock programs as a central element, and the action group has mounted a very active campaign to influence the creation of comprehensive mandatory interlock laws in all states and provinces. A survey of manufacturers conducted in May/June 2006, and then 18 months later in September 2007, determined that the installed base of interlocks rose about 35% from an estimated 100 000 units to 135 000 in the USA. Prior to 2006, interlock devices had been available for 20 years in North America and, with the exception of a few jurisdictions where installation rates exceed 25% (e.g., New Mexico, Florida, and Quebec), the overall installation rate relative to DWI arrests had been about 5%, not nearly enough to have a significant direct impact on DWI or a particularly important

impact on general deterrence. Accordingly, 2006 may mark the start of a significant growth period. New Mexico may serve as a model for other states, having passed five mutually supportive interlock laws in the six years between 1999 and 2005.

Since 2005, with minor exceptions, New Mexico state law requires that the courts order all DWI offenders to install interlock devices (not all courts comply with the state law and not all offenders comply with the court order). In addition, New Mexico also has a licensing law that permits DWI offenders (who are still in license revocation status from earlier offenses before the new laws) to install and drive with a special interlock license even though the regular license is still formally revoked. Accordingly, with both a court program and an administrative option for interlock installation, New Mexico has the highest installation rate (per capita) in North America; the major population centers in Albuquerque and Santa Fe have also succeeded in attaining installation rates by DWI offenders of more than 50%.

The Florida program in the United States has also attained a high rate of installation among eligible offenders (86%), but the path to eligibility in Florida is very long and as of yet, many of the DWI offenders (likely the most difficult offenders) do not qualify. As of 2006, 51 043 offenders were required to install interlocks in Florida, but only 15 181 had become eligible, and the 86% rate reflects the 13 112 who had actually installed the interlock; of the total number, the installation reflects a 26% rate [8]. This is still very good for a program managed by the licensing authority rather than the courts, but time will tell if the law will lead to more interlocks, or more driving with a suspended license by the other 74% who have not yet become eligible to install an interlock.

Whether interlock programs can help public policymakers achieve the goal of substantially reducing alcohol crashes will remain uncertain until procedural barriers and changing judicial practices allow for more routine use of the interlock. There exists somewhat of a philosophical difference among different interlock program types. Some court programs may insist on abstinence and full compliance with an order to no longer drink, whereas others are more centrally focused on reducing impaired driving and are less concerned about drinking habits that do not endanger the public on the roads.

Despite strong effectiveness evidence in all studies to date, the real potential of this technology to reduce the road toll cannot be estimated with certainty until interlocks are more widely adopted. What is the best way to increase the installed base? Canada's programs are all administrative (managed by the licensing authority) and many US states have adopted that approach as well. However, the courts have stronger powers of persuasion. A court in Hancock County, Indiana, in the United States was found to have achieved an installation rate of 62% by making the interlock an alternative to jail (via house arrest if the interlock was not installed) [9]. High rates like this are the exception, however. Some people see the judiciary as the primary barrier in the USA because change is embraced very slowly by the courts, partly because there are so many individual judges and prosecutors who need to be educated. For example, DeYoung [10] reported that just 10% of eligible

DWI offenders in California were ordered by the courts to install an interlock, and only 22% of those complied, a net yield of about 2.2%. This may have started to change in the USA; in 2007 the administrator of NHTSA took an active role in bringing opinion leaders together to improve judicial education about the contribution alcohol sensing technology can make to road safety.

For offenders who defy the court and drive without a license after a DWI results in license suspension, one option is to require the use of ankle bracelets that detect drinking through sensing of the alcohol vapor that is released from the skin surface. These transdermal alcohol sensing devices, SCRAM (Secure Continuous Remote Alcohol Monitoring) lock on the ankle and can serve as a more restrictive alternative to interlock programs for the recalcitrant repeat offender. SCRAM effectively detects more than minimal drinking, and within 24 hours or less any lapses of self-control will be identified by a monitoring authority *via* SCRAM's wireless link. The device communicates nightly to a telephone modem that uplinks and reports the past 24 hours of performance to a remote server. Evaluation studies have documented the accuracy of these devices [11, 12], which are worn 24 hours a day, often for months at a time without removal.

The following sections review some of the procedures and evidence that warrants interest in alcohol ignition interlock devices, or "alcolocks" as they are referred to in some European nations.

Device standards, program guidelines

The current alcohol interlock systems consist of a breath-testing device linked to the vehicle ignition system that requires the driver to provide a breath sample every time an attempt is made to start the vehicle. The interlock device prevents the vehicle from being started unless the driver provides a sample that reveals an alcohol concentration lower than a threshold value – often 0.02 g/dL, but up to 0.040 g/dL; the 1992 US NHTSA Guidelines suggested 0.025 g/dL. Florida has an unusually high lock point at 0.051 g/dL. In the event the breath sample reveals a BAC in excess of the threshold value, the interlock prevents the vehicle from starting and the driver must wait some minutes before trying again. In most applications, after several failed attempts the interlock goes into an extended lockout period.

At least four government agencies have established standards or guidelines for interlock devices [13–16]. NHTSA guidelines have been undergoing revision for the past several years and are expected to be released with updated requirements in 2008; NHTSA has also been working on a set of interlock program guidelines [17]; Transport Canada released a set of draft standards in 2007 for interlock devices [18], and similarly Canada has been developing program standards [19] as well. Devices that meet these standards provide assurance to both the public and the users that the devices perform as expected and desired. For example, unlike an earlier interlock, the current generation of interlock devices use a fuel-cell sensor that is specific to

alcohol (i.e., these eliminate false-positive readings due to other organic hydrocarbons as often occurred with the original Tagucci Cell semiconductor devices) and the newer devices can more reliably prevent engine ignition in extreme weather and differing atmospheric pressure conditions.

Concern continues to be expressed about the possibility of circumventing the device by tampering with the circuitry, introducing a bogus air sample, or filtering the sample to remove some of the alcohol. Protection against potential circumvention of the device is also required by government standards. To meet these standards, depending on the jurisdiction, interlock devices contain such features as temperature and pressure sensors (to guard against filtered or stored samples or samples introduced by mechanical devices), unique hum codes or suck/blow sequences, a data recorder (to log all attempts to start the vehicle and to record the driver's BAC), and a running retest requirement (to limit the benefit if a non-occupant bystander were to provide a startup breath sample and to limit the benefit of leaving the car idling for extended periods).

These features have helped to create an interlock device that does prevent drivers impaired by alcohol from operating the vehicle. Although most interlocks are accurate in a range of operating environments, these are not field forensic test devices; they are simply expected to prevent impaired driving – and in general they do. The more difficult challenge is setting the program features that are built to support the device and which specify common procedural and administrative operating guidelines.

As distinct from the device guidelines, some of the items under consideration in the Canadian and/or the US program guidelines will address the following questions:

- Should someone be extended for a longer period on the interlock? When (what are the triggers) to extend someone? How long an extension?
- How to mark the driver's license so the police are aware of the interlock restriction?
- How often should the interlock provider report to the court or licensing authority, and what types of information should be in those reports?
- What to do about positive breath tests (if anything)? Some jurisdictions see positive BAC tests that lock out the ignition preventing a start-up as evidence that the interlock is working as intended and no action is needed. Others (often court programs) see these positive tests as evidence of a violation of the court order to cease drinking and this leads to possible further sanctions.
- How shall neighboring jurisdictions handle the problem of DWI arrests of drivers under interlock restrictions?
- How to help pay the interlock costs for indigents?
- What should be done about those with reduced lung capacity?
- How shall the interlock program communicate with the general public to build support for the program?
- What should be key features of an anti-circumvention protocol?

Interlock programs' efficacy and effectiveness

Since the first interlock program was introduced in California more than 20 years ago, several studies have evaluated the effectiveness of using interlocks as a means to incapacitate convicted DWI offenders and prevent repeat DWI offenses. Table 1 summarizes the results of the evaluation studies of interlock programs published to date.

All of the evaluation studies of alcohol ignition interlock programs have methodological limitations. Evaluations have come from several US states (California, Colorado, Illinois, Maryland, New Mexico, North Carolina, Oregon, Ohio, and West Virginia), two Canadian provinces (Alberta and Quebec), and Sweden. Only one study [26] has been a random assignment study, with a sample selected and approved for research by a medical review board. Regardless of methodology, however, the results of the published studies have been largely consistent; Table 1 summarizes the literature relevant to the efficacy of interlock devices both while installed and after removal relative to non-interlock contrast samples. A data combining meta-analysis of 13 studies calculated a 0.36 relative risk of repeat offense DWI while the interlocks were installed and also confirmed the position stated in 2001 by the ICADTS working group [1] and others [34] that there is little risk reduction carryover into the period once the interlocks are removed [2]. Like all others who investigate interlocks, these authors concluded that the evidence for real effectiveness will require a greater rate of uptake with interlocks fitted onto the vehicles of the full range of DWI offenders.

There is probably some degree of self-selection among those who come into the interlock groups that cannot be fully controlled by equating for age, gender, number of prior DWIs, and the other few variables that may be available in a driver record file. Research studies available for evaluation in areas related to criminal justice rarely conform to the requirements of a random clinical trial. Courts are required to dispense justice fairly, not randomly, and as a result mutually agreeable, well designed study plans are often overruled by a judge after a study has begun. The Cochrane Collaboration rules are an excellent ideal but are often not very practical in evaluation studies involving legal matters, especially when judicial and prosecutorial decisions can be challenged by defense litigation or be influenced under the pressure of local elections. Evaluation of road safety policies and programs will usually be constrained by a variety of factors, including the type and quality of data available, inability to exercise control over and/or account for extraneous events, and the difficulty in obtaining adequate comparison groups. This is a simple reality of applied safety research, and these constraints are not unique to interlock studies.

The almost uniformly positive findings from evaluation studies on the interlock programs that have been conducted across different populations of offenders for various lengths of time suggest that the effects of the interlock programs are robust. The type of population and the magnitude of the effect, however, vary considerably. DWI offenders with more to lose are inevitably more likely to comply with the program requirements. Evidence is needed that the highest risk cohorts can be

Table 1 Summary of Interlock Evaluation Studies[1,2].

Authors/Year	Jurisdiction	Characteristics of population	Findings: Recidivism with interlock	Findings: Recidivism after interlock	Comparison Group
EMT Group (1990) [20]	California	First and multiple	Interlock 3.9% Noninterlocks 5.9%	----------	Suspended
Elliott & Morse (1993) [21]	Cincinnati, Ohio	First offenders over .20% BAC plus multiple offenders	Interlock 2.9% Noninterlocks 8.4%	Interlock 6.6% Noninterlocks 6.5%	Suspended
Jones (1993) [22]	Oregon	Multiple offenders	Interlock 5% Noninterlocks 8%	Interlock 10.8% Noninterlocks 11.5%	Restricted
Popkin, Stewart, Beckmeyer, & Martell (1993) [23]	North Carolina	Second offenders	Interlock 2.7% Restricted 7.1% Suspended 9.8%	Interlock same or higher than noninterlock	Restricted license & suspended
Weinrath (1997)[24]	Alberta	Multiple offenders	Interlock 10% Noninterlocks 25%	Interlock 7% Noninterlocks 11%	Suspended
Tippetts & Voas (1997) [25]	West Virginia	First and second offenders	Interlock 1.6% Noninterlocks 6.4%	Interlock 10% Noninterlocks 10%	Licensed & suspended
Beck, Rauch, Baker, & Williams (1999)[26]	Maryland (random assignment)	Second offenders	Interlock 2.4% Noninterlocks 6.7%	Interlock 3.5% Noninterlocks 2.6%	Licensed
Voas et al. (1999) [27]	Alberta	First offenders	(12 months) Interlock 0.1% Suspended 2.23% Ineligible 4.61%	Interlock 2.75% Reinstated 2.63% Still Suspended 2.48%	Reinstated & ineligible

Table 1 *(continued)* Summary of Interlock Evaluation Studies[1,2].

Authors/Year	Jurisdiction	Characteristics of population	Findings: Recidivism with interlock	Findings: Recidivism after interlock	Comparison Group
		Multiple offenders	(24 months) Interlock 0.85% Suspended 8.08% Ineligible 18.72%	Interlock 7.05% Reinstated 7.32% Still Suspended 3.94% Ineligible 10.52%	Reinstated & ineligible
Vezina (2002) [28]	Quebec	First & repeat offenders	1st (12 months) Interlock <0.5% Suspended 2% 2nd (24 months) Interlock <2% Suspended 6%	1st (24 months) Interlock 4% Suspended 5% 2nd (36 months) Interlock 4% Suspended 7%	Suspended
Raub, Lucke, & Wark (2003) [29]	Illinois	Multiple	Interlock 1.3% Restricted 6.8%	Interlock 1.7% Restricted 2.0%	Restricted
Bjerre (2003) [30]	Sweden	First & Multiple	Interlock 0% Revoked 2.9% Matched 1.6%	----------	Revoked & matched
Roth, Voas, Marques (2007) [31]	New Mexico	Mandated multiple offenders	(12 months) Interlock 3.3% Noninterlock 10%	(12 months) Interlock 10% Noninterlock 10%	Revoked and matched
Roth, Voas, Marques (2007) [32]	New Mexico	First Offenders	(12 months) Interlock 2.6% Noninterlocks 7%	(12 months) Interlock 4.9% Noninterlock 6.7%	Revoked & matched

[1] Source: Amended from Beirness & Marques [33].

[2] Some rates read from charts and are therefore approximate.

more effectively managed with an interlock (or other control technologies). Most studies fail to enroll the very high-risk cohorts but as penetration increases this may become a problem of the past. For example, evidence accumulating in New Mexico shows that as interlock penetration has increased there have been reductions in DWI arrests, alcohol-crashes, alcohol-crash injuries, and a trend toward reduction in alcohol-related fatalities (Fig. 1). Although interlocks are not the only intervention underway in New Mexico, and a causal link between interlock increase and fatality decrease cannot be assumed, the interlock program is nevertheless the most prominent intervention and receives widespread media coverage. Figure 1 shows the temporal relationship between the increase in interlocks (solid line) and the decline in DWI fatalities (dashed line) during the five years before and the five years after the 2002 mandatory interlock law. New Mexico had relatively little interlock uptake after its voluntary 1999 law, it was not until the 2002 mandatory law for repeat offenders that rates went up, and with the 2005 mandatory law for all offenders the increase was sustained [35]. New Mexico has the highest rate of interlock penetration of any state in the United States (36/10 000), exceeding by more than double the per capita installation rate of Washington, the state with the next highest penetration rate.

Despite the apparent beneficial impact of interlock programs, as noted earlier there is very little residual prevention of impaired driving after the device is removed or, at best, for a limited time thereafter. This should not reflect poorly on the efficacy of interlock programs but rather the difficulty of real behavior change, a problem that is quite familiar to the psychological services community. There are no quick fixes to deeply ingrained habits. Long-term behavior change is an elusive goal of many countermeasures and sanctions, including license suspension and jail. Not all, but many DWI offenders, including those who participate in interlock pro-

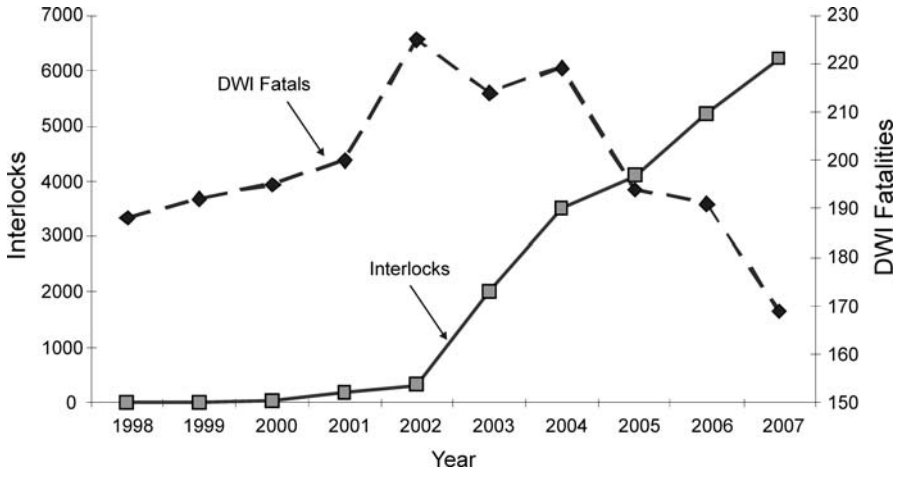

Figure 1 New Mexico: Interlocks and DWI fatalities by year since 1998.

grams, have behavior consistent with DSM-IV (or ICD-10) clinical diagnoses of alcohol dependence or at least abusive or hazardous drinking. The installation of an interlock does not change this; it just prevents the individual from operating the vehicle after drinking. Interlocks were never intended as a treatment for alcohol abuse; therefore, it should not be expected that an interlock device will, by itself, reliably cue a change in the extent of alcohol consumption. Also, there is some evidence that repeat offenders may be less capable of benefiting from conventional intervention services. Glass, Chan, and Rentz [36] reported that, in an evaluation of 134 second-offender volunteers, 73% tested as having one or more significant cognitive impairment. Special treatment services that can work with short attention spans, poor memory, and poor impulse control may be needed to help this sub-population. Treatment services for alcohol dependence should improve success rates if treatment plans and monitoring are integrated with the alcohol interlock data record to promptly detect and deal with lapses in alcohol control or abstinence.

Interventions and approaches to monitoring the participants

Research studies have taken two approaches to strengthen the interlock experience for long-term benefit. These steps include (1) improving the quality, immediacy, and appropriateness of *counseling intervention services* while an offender is the "captive" of an interlock program, and (2) improving the *predictive models* so the judicial or motor vehicle authority can anticipate which offenders pose the highest risks to the public if they became fully relicensed and are no longer controlled by an interlock program. The ability to predict high-risk offenders is greatly improved by using data captured in the interlock's recorder, which logs every start attempt and BAC test result while the interlock is in use.

Counseling intervention services

Marques, Tippetts, Voas, Danseco, and Beirness [37] reported results from a two-city comparison in which 610 interlock offenders in Calgary, Alberta, received an adjunctive intervention during each monthly visit to the interlock service center, whereas 747 offenders in the Edmonton area did not. Edmonton, Alberta, is a city of comparable size and approximate demographic makeup. The intervention was a composite of motivational enhancement, pragmatic counseling, and anticipatory planning for life after the interlock [38]. Among those in the intervention site, a 50% reduction in recidivism rates of first offenders relative to the comparison first offenders was found during the first 12 months after the interlock was removed (odds ratio = 0.46). No comparable effect was documented for multiple offenders. Because intervention and city varied together, it is not possible to confidently attribute the difference to the intervention protocol. It suggested, however, that behavior

can be affected, at least temporarily, to slow the return to impaired driving after the interlock. In that study, the intervention could not be uniformly applied to all interlock clients since they were not ordered by the court to participate. More than 80% agreed to be in the study, but once in, commitment to the program varied widely.

In an effort to deliver a more systematic and fully specified intervention protocol, a motivational enhancement intervention for interlock offenders was devised and built around the motivational model [39] in Texas. In this case, the sentencing judges required the offender to install the interlock and to attend the *SIP (Support for Interlock Planning)* intervention. The intervention combined 12 hours of services delivered in both group and individual session formats. The protocols are fully specified with Provider Manuals in English and Participant Manuals in English and Spanish [40, 41] and can be found online at http://www.pire.org/SIP/SIP-Manuals.htm.

While the contrast group could not be equated to the SIP group, participants in the *SIP* intervention had significantly fewer elevated BAC tests than those who did not participate ($P < 0.03$). In addition, evidence from pre-post survey instruments (Drinkers Inventory of Consequences [42], and the Alcohol Use Disorders Inventory [43]) showed significant changes in drinking level and drinking consequences following the intervention [44]. Satisfaction survey items suggest this pragmatic model of reconsidering the costs and benefits of drinking and driving appeals to the offenders. Whether this translates into a reduction in impaired driving has not yet been determined. This kind of evidence suggests that an interlock program linked to a pragmatic motivational enhancement intervention may reduce the risk of post-interlock recidivism. This kind of program will not be appropriate for all interlock offenders, but for some it may help reinforce the behavior change that is initiated through interlock control.

Predictive modeling: Who are the highest risk offenders?

The record of interlock BAC tests

We have reported that the rate of elevated interlock BAC tests strongly predicts the likelihood of future impaired driving convictions during the first two years after the interlock is removed. This finding was first documented in Alberta from data of 2 200 offenders who provided 5.5 million BAC tests [45], subsequently confirmed in Quebec with 7 200 offenders based on 18.8 million breath tests [46]. The rate of interlock BAC tests that are elevated above 0.02 g/dL relative to all tests taken strongly predicts repeat DWI likelihood. An evaluation of the relative potency of this effect relative to other known predictors of repeat DWI offenses found it to be the first or second best advance indicator [47] – better than moving violations, driving-while-suspended charges, demographic and questionnaire-based information and, depending on the sample, better than prior DWI offenses. This predictor, based on elevated interlock BAC tests, has particular merit for first-time DWI offenders,

among whom there is often little advance indication of whether an individual will pose a public hazard if he or she receives an unrestricted license.

In addition, the occurrence of elevated tests during the morning hours adds substantially to a predictive model for future DWI offenses. While the overall highest number of BAC tests taken occurs in late afternoon around 5:00 P.M., the highest number of tests with BAC $\geq$0.02 g/dL occurred between 7:00 and 9:00 A.M. on weekdays (Monday–Friday). This early morning weekday pattern of the highest number of elevated tests was originally found in the Alberta and Quebec data and later confirmed in the Texas interlock data from more than 10 000 offenders [48]. These positive BAC tests reflect the unmetabolized ethanol from a prior night of drinking and, therefore, can serve as unobtrusive indicators of binge drinking the prior night. In Alberta and Quebec, knowing which offenders logged two or more elevated BAC tests during the morning hours strengthened the predictive model by another 45% after accounting for all other factors [46, 47], including prior DWI status.

Alcohol biomarkers

Other advance indicators of drinking problem level still need to be available because the interlock is a vehicle sanction and other people are permitted to drive the car. Alcohol biomarkers have seen virtually no systematic use in North America but are increasingly used in Europe [49, 30, 50] as part of driver fitness decisions. These biomarkers, such as carbohydrate deficient transferrin (CDT) or gamma glutamyltransferase (GGT), are durable indicators of ethanol exposure that can be measured in blood from days to several weeks after drinking. People with high levels of exposure and with consumption of five or more drinks per day (60 gm ETOH) for a week will activate one or more of these indicators. Direct ethanol metabolites, such as phosphatidyl ethanol (PEth) [51] found in blood and ethyl glucuronide (EtG) [52] found in urine, serum, or hair, are generating much interest as indicators of relapse in patients who are undergoing ethanol dependence treatment or who are chronically exposed to alcohol. In addition to EtG, other byproducts of ethanol metabolism, such as fatty acid ethyl esters (FAEE) sequestered in the growing hair shaft, provide promising new assessment tools to document exposure [53] and, in time, may add useful risk indicators to relicensing decisions. Recent research by Marques et al. [54] has shown that elevation of PEth and GGT are strongly and significantly correlated with the rate of elevated BAC tests from the interlock records of DWI offenders.

The major difficulty with all of these novel technological approaches to detecting driver risk or intervening to rehabilitate drivers is the importance of finding a way to do so without forcing more high-risk drivers out of compliance and into the decision that it is simply easier to take a chance and to drive while suspended or revoked. However, it is very clear that the interests of the alcohol treatment community and the public safety community can be more fully joined around the alcohol

interlock, whether the motive is to rehabilitate the individual, improve road safety by preventing injury of the innocent, or both. Alcohol ignition interlock devices are simply a form of vehicle incapacitation (i.e., an electronic device intended to prevent a reoccurrence of drinking – driving behavior). But when used as an electronic monitor, it is fully in the traditional of other forms of behavioral monitoring. Adding alcohol biomarkers to the decision matrix will enable the rehabilitation community to triangulate in on drivers most in need of intervention and who pose the greatest risk to the driving public.

Thinking differently about DWI

One barrier to more widespread adoption and implementation of interlock programs is the criminal justice perspective on the DWI problem in the United States. Over the past two decades, much effort has been devoted to convincing the general public, legislators, administrators, policymakers, and judges of the seriousness of alcohol impaired driving behavior. The results of these efforts have been numerous legislative amendments increasing the severity of sanctions for a DWI conviction. Acceptance of interlock programs as a form of public protection rather than criminal retribution requires an adjustment to this punitive framing. Short of jail or electronic house arrest, there are few effective ways to enforce long periods of license suspension. If there were, unlicensed driving would not be among the largest problems confronting the highway safety community. In California, only 16% of offenders even bothered to reinstate their licenses within a year of their eligibility [55]. The risk of detection or apprehension is very low; seventy-five percent of DWI offenders report driving without a license [56]. There are more than one million unlicensed drivers operating in California.

As a historical note, getting the courts and motor vehicle authorities to adopt license suspension following a DWI offense represented an important achievement of the safety community years ago. Previously, DWI charges were not taken very seriously at all. But now, license suspension is embedded as a cornerstone sanction for DWI offenses. When traffic density was lower and the perception of risk higher, license suspension made more sense. But, a belief that license suspension is the key effective sanction has fueled a continuous push in the direction of ever-increasing lengths of license suspension. For a brief period in Ontario, Canada, after the year 2000, a third-time DWI offense resulted in a lifetime suspension that might, if conditions were met, be reduced to 10 years. There is little evidence that identifies the optimal length of license suspension or the effectiveness of longer *versus* shorter periods of suspension. On the other hand, it appears that suspended drivers quickly learn that the probability of being caught driving while suspended is exceptionally low. With the high reconviction rates among the suspended control groups in interlock evaluation studies, it is evident that many suspended drivers drink as well as drive illegally.

Within some segments of the legal community, there is a move to more actively embrace "therapeutic jurisprudence." This is an approach that grows from the understanding that society is best served when our institutions can facilitate more cooperative human behavior, in this case abiding by the safety laws. Interlock programs may be able to serve the interests of both the sanctioning and the helping functions of society [57]. For example, the most advantageous use of interlocks may be less as a punishment for past DWI offenses and more as a shield to protect the public. Although there are punitive aspects of participating in an interlock program, the primary goal is incapacitation (i.e., it serves to prevent subsequent offenses by placing a physical barrier between the drinker and the operation of the vehicle). As the New Mexico evidence has shown, interlocks can co-exist with license suspensions. In fact, interlock programs can actually extend the time offenders are under some sort of supervision and control – either by the courts or the licensing authorities. At the same time, however, the interlock allows offenders to drive when they have not been drinking. It is this latter aspect of interlocks that goes beyond traditional notions of crime and punishment. It is a compromise that recognizes that mobility is often a necessity to participate in a modern economy.

Acceptance of interlock programs requires that administrators, judges, policymakers, and others relax their exclusive reliance on the criminal justice perspective for dealing with DWI offenders; they should focus less on punishing offenders and more on incapacitation, rehabilitation, and public safety. Drinking and driving is a problem that lies at the intersection of the punishing and helping branches of society. Treating DWI as solely a criminal problem squanders an opportunity to bring more of our societal capabilities to resolve it. An interlock program may be an ideal bridge technology.

Conclusion

Nearly 25 years beyond their initial field trials in several California counties, interlock devices and programs have reached a high level of maturity. Penetration into state and provincial legislation in the United States and Canada has been thorough, and supporting federal legislation has endorsed them in both countries. Following the North American evidence and Sweden's move to embrace a national interlock program, the European Union has moved forward and implemented several field trials. The French program continues to expand. The Australian State of Victoria has a very active, high penetration, interlock program as well. The devices *per se* have attained an adequate level of maturity and sophistication. The programs (including: the laws, the procedures, the reporting requirements, the administrative protocols, the user support systems) continue to be a work in progress. Interlock penetration continues to be a problem, and interlocks will not contribute substantially to risk reduction until the programs are more widespread. In the United States, based on the somewhat unreliable FBI estimate of 1.4 million DWI arrests/yr, and the September

2007 estimate of 135 000 installed interlocks; about 10 % of DWI arrests now result in interlocks.

As the growth continues, researchers will need to continue to evaluate interlock effectiveness evidence to determine if interlock programs can reduce recidivism systemwide, not just in small programs. No one has yet unequivocally documented an overall alcohol crash reduction specifically due to interlocks, although alcohol-related crashes are almost certainly reduced where interlock penetration is high. Much more needs to be done to enhance the impact of interlock programs through integration with other countermeasure programs, most notably alcohol treatment, rehabilitation, and monitoring.

The widespread adoption of interlock programs may require some revision of the traditional criminal justice approach to dealing with DWI offenders. Strongly punitive sanctions that impose barriers on licensed driving create an incentive for unlicensed driving. The interlock allows for socially responsible behavior such as driving to work and participating in family life. For those who feel it is important to punish DWI offenders, they should realize there are significant punitive aspects to the interlock. They are inconvenient and often embarrassing, and they impose a monetary cost on the offender equivalent to about $2.25/day. In most implementations of the interlock, the driver must blow a running breath sample on an average of about every 30 minutes.

An interlock program also requires some level of administrative control and monitoring. Our research has shown that motivational intervention programs linked to an interlock can make good use of the dual functions of control and monitoring that are part of the interlock program. Alcohol-impaired driving is a problem in nearly all societies of the world. All struggle with different local features of the problem, but ultimately, we all would like to rehabilitate the drinker, whether for humanitarian or pragmatic reasons, because that will help improve the public good. An approach that incorporates a balance of sanctions, incapacitation, and rehabilitation may help us achieve both safety and humanitarian objectives. DWI is a problem that exists at the intersection of health behavior and criminal behavior; we will benefit if our societal approach recognizes both parts of it and intervenes appropriately.

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Dose related risk of motor vehicle crashes after cannabis use: an update

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Abstract

Experimental studies have repeatedly shown that THC impairs cognition, psychomotor function and actual driving performance in a dose-related manner. The degree of performance impairment observed in experimental studies after doses up to 300 μg/kg THC were equivalent to the impairing effect of an alcohol dose producing a blood alcohol concentration ≥0.05 g/dl, the legal limit in most European countries. Higher doses of THC have been shown to produce even larger impairment. Highly automated behaviors were more affected by THC compared to more complex driving tasks requiring conscious control. Epidemiological findings on the role of THC in vehicle crashes have sometimes contrasted findings from experimental research. Case-control studies generally confirmed experimental data, but culpability surveys showed little evidence that crashed drivers who only used cannabis are more likely to cause accidents than drug-free drivers. However, most culpability surveys have established cannabis use by determining the presence of an inactive metabolite of THC that can be detected for days after smoking and can only be taken as evidence for past use of cannabis. Surveys that established recent use of cannabis by directly measuring THC in blood showed that THC positives, particularly at higher doses, are about 2–7 times more likely to be responsible for their crash compared to drivers who had not used drugs or alcohol. Together these epidemiological data indicate that recent use of cannabis increases crash risk, whereas past use of cannabis does not. Experimental and culpability studies have demonstrated that performance impairment and crash risk increase as a function of THC concentration. Moreover, performance impairments as assessed during acute THC intoxication in experimental performance studies were highly correlated to THC-induced crash risk in culpability studies. Experimental and epidemiological research provided similar findings concerning the combined use of THC and alcohol in traffic.

Introduction

The effects of Δ^9-tetrahydrocannabinol (THC) on the ability of drivers to operate safely have traditionally been determined in epidemiological surveys of THC users' involvement in traffic accidents and in experimental studies to measure the drug's influence on skills related to driving [1–8]. The purpose of epidemiological studies is to determine both the severity of THC impairment and the prevalence of THC use among the driving population by measuring the frequency of cannabis use among drivers who do and do not become involved in crashes. Essentially they aim to determine if cannabis use is over represented among drivers who were involved in accidents. Experimental studies are designed to predict the effects of cannabis on driving ability by measuring their users' performances in laboratory tests of isolated psychological functions, driving simulators and on-the-road driving tests. In the context of well-designed experiments, drugs that produce large performance impairments in many different tests can be considered potentially hazardous to drivers whereas drugs that fail to produce any impairment can be considered safe. Experimental studies often provide the earliest evidence for a drug's hazard potential for driving.

Many excellent studies on the effects of cannabis on driving are available only as technical reports, proceedings or book chapters. That is unfortunate, since reviews in general should not cover data that are not published in peer-reviewed sources. Yet, applying this rule invariably would seriously weaken any review in this field. We therefore decided to also include sources that did not appear in peer-reviewed formats, i.e. about 50 % of the references, in order to fully summarize and integrate what is known about the effect of cannabis on performance and driving ability. In particular a summary of the literature relevant to the following research questions will be given:

- Does cannabis impair psychomotor, cognitive and actual driving performance and increase the risk of becoming involved in traffic accidents?
- Is there a relation between performance impairment and cannabis dose or its concentration in plasma?
- Do combined effects of cannabis and alcohol on driving performance differ from those of either drug alone?
- Does cannabis affect all aspects of the driving task alike?

Epidemiological studies

Prevalence of thc in crash involved drivers

Surveys conducted in widely separated localities have generally revealed the presence of THC in between 4–14 % of drivers who sustained injury or death in traffic accidents [9–21]. Occasionally higher values have been reported for groups of, predominantly, young males operating in one or another large American city [22–24].

These data however cannot be accepted as evidence showing that THC was responsible for the crashes, even though the prevalence of THC in the general driving populations is assumed to be lower. The reason is that alcohol was also found in 50–80 % of the same drivers. It is highly likely that combination of THC and alcohol poses a bigger risk potential than those of either drug alone. An additional limitation of these surveys is their lack of an appropriate control group. Prevalence studies indicate the extent to which substances such as THC and alcohol are present in the blood of (fatally) injured drivers. In the absence of comparable data from an appropriate control group selected from the general driving population, results of prevalence studies can never be taken to indicate the role of THC or other drugs in causing traffic crashes.

Culpability studies

Epidemiologists have tried to overcome the lack of normative data from the general driving population by analyzing the culpability index of drivers involved in traffic accidents. Basically, they distinguished between drivers that were responsible for their crash and those who were not. The former are taken as the cases and the latter as controls, for determining the odds ratio for responsibility for traffic accidents under the influence of cannabis. Classification of culpability should, of course, take place without knowledge of the drugs/alcohol status of drivers in order not to bias the classification process.

There have been several culpability studies that investigated the association between cannabis, alcohol and traffic crashes. A summary of these studies and their measure of association is summarized in Table 1. ORs and 95 % CIs presented in Table 1 are taken from the original study reports or adapted from Bates and Blakely's [4] re-analyses of these data. It is important to note that in this type of analysis the crash culpability rates among drivers positive for THC are compared to crash culpability rates in drug (including alcohol) free drivers. The odds ratio of drug free drivers to become involved in a traffic crash is set to 1.0, and serves as the point of reference in order to determine the statistical significance of changes in odds ratios for drivers under the influence. If this reference value of 1.0 falls outside the 95 % CI associated with odds ratios for a certain drug, we can safely conclude with 95 % certainty that this drug significantly affected crash culpability. However, if the 95 % CI includes the reference mean, the conclusion must be drawn that crash culpability rates of drugged drivers are comparable to crash culpability rates in drug-free drivers.

All culpability studies have shown that alcohol and the combination of alcohol with cannabis significantly and strongly elevated crash culpability rates. In most studies the combined effects of cannabis and alcohol on crash culpability appeared additive, although a weak suggestion of a synergistic effect was also apparent in some. Yet, most culpability studies [10, 11, 22, 25–28] also seem to indicate that cannabis alone does not increase crash culpability. However, these culpability studies have identified cannabis use among drivers by solely measuring THC-COOH,

an inactive carboxy metabolite of THC [22, 25–28] or by measuring either THC or THC-COOH [10–11]in blood or in urine. Following the use of cannabis, THC-COOH may be present in blood or urine for days. The presence of THC-COOH thus does not necessarily imply recent use of cannabis or impairment. Recent exposure to cannabis can only be safely assumed in the minority of culpability studies that determined cannabis use by the presence of THC in the blood.

Only three culpability studies [26, 29, 30] determined recent cannabis use by assessing THC in blood. While using identical methods for establishing culpability of the driver these studies generally showed that crash culpability for THC positive cases increased with rising concentrations of THC in blood (see Table 1). The study by Hunter et al. [26] (also published in Longo et al. [31]) in 2500 injured drivers failed to establish a relation between relatively low concentrations of THC and driver culpability but did find that culpable drivers had a higher mean THC concentration, a difference that approached statistical significance ($p = 0.057$). Drummer et al [29] also reported that increments in crash responsibility rates were most prominent at high concentrations of THC. They conducted a responsibility analysis in 3398 Australian fatally injured drivers recorded in their database between 1990–1999. THC was present in 58 cases in which no other psychoactive drug or alcohol was found. The median THC concentration was 10 ng/mL with a range from 1–100 ng/mL. THC positive cases showed an OR of 2.7 compared to drug free drivers, while taking into account interactions for age, gender, crash type, jurisdiction and year of collection. The range of the confidence interval strongly suggested significance of the OR value as it did not include the reference value 1.0. Analyses on a subset of cases with THC concentrations of 5 ng/mL or higher revealed a culpability ratio of 6.6 in THC driver fatalities as compared to drug free cases. Since alcohol was a common factor found in cannabis positive cases, the effect of THC and alcohol combined was also evaluated relative to drivers who were only positive to alcohol (i.e. blood alcohol concentration (BAC) > 0.05 g/dl). This analysis revealed a significant increment of crash risk (OR 2.9; 95% CI: 1.1–7.7) suggesting that THC does enhance alcohol-induced impairment, and that this impairment is at least additive to alcohol.

The culpability study by Laumon et al. [30] arose from a unique political situation in France. The French government intended to install drug-driving legislation and funded a large scale epidemiological study to determine the association between cannabis and crash risk. In addition, it temporarily allowed compulsory urine and blood testing of all drivers ($N = 10\,748$) who were involved in fatal crashes in France from October 2001 to September 2003. The cases were 6766 drivers considered at fault in their crash and the controls were 3006 drivers selected from those who were not at fault. The authors provided odds ratios as a range of values taking into account a range of confounding factors (i.e. alcohol, age, type of vehicle, type of accident) or not. Their data demonstrated that cannabis use was significantly associated with a concentration dependent increment in culpability risk. When unadjusted, or only adjusted for alcohol, significant increments in crash risk were already prominent at very low THC (i.e. < 1 ng/mL) concentrations. When adjusted

Table 1 Summary of minimal and maximal reported OR of becoming involved in fatal or injurious traffic accidents under the influence of cannabis, alcohol or their combination as reported in culpability studies. Significance of changes in OR is indicated as follows: * < 0.05.

Substance	Authors	Odds ratio	95 % CI
Drug free cases		1.0	
Alcohol	Terhune & Fell (1982);	5.4 *	2.8–10.5
	Williams et al. (1985);	5.0 *	2.1–12.2
	Terhune et al. (1992);	5.7 *	5.1–10.7
	Drummer (1994);	5.5 *	2.2– 9.6
	Hunter et al. (1998);	6.8 *	4.3–11.1
	Lowenstein & Koziol-McLain (2001);	3.2 *	1.1–9.4
	Drummer et al. (2004);	6.0 *	4.0–9.1
	Soderstrom et al. (2005)	7.5 *	5.1–10.8
THC-COOH	Terhune & Fell (1982);	2.1	0.7–6.6
	Williams et al. (1985);	0.2	0.2–1.5
	Terhune et al. (1992);	0.7	0.2–0.8
	Drummer (1994);	0.7	0.4–1.5
	Hunter et al. (1998);	0.9	0.6–1.4
	Lowenstein & Koziol-McLain (2001);	1.1	0.5–2.4
	Soderstrom et al. (2005)	1.2	0.8–1.6
THC (ng/mL whole blood)			
< 1.0	Hunter et al. (1998);	0.35	0.02–2.1
1.10–2.0	Drummer et al. (2004);	0.51	0.2–1.4
> 2	Laumon et al. (2005)	1.74	0.6–5.7
1–100		2.7*	1.02–7.0
5–100		6.6*	1.5–28.0
(adjusted for alcohol)			
< 1		1.9 *	1.0–3.5
1–2		2.0 *	1.5–2.8
3–4		2.8 *	1.6–4.8
> 5		3.1 *	1.9–3.0
(adjusted for alcohol, age, vehicle type, time of crash)			
< 1		1.6	0.8–3.0
1–2		1.5 *	1.1–2.2
3–4		2.1 *	1.2–3.7
> 5		2.1 *	1.3–3.4
Alcohol/THC or THC-COOH	Williams et al. (1985);	8.6 *	3.1–26.9
	Terhune et al. (1992);	8.4 *	2.1–72.1
	Drummer (1994);	5.3 *	1.9–20.3
	Hunter et al. (1998);	11.5 *	4.6–36.7
	Lowenstein & Koziol-McLain (2001)	3.5 *	1.2–11.4

for the full range of confounding factors, odds ratios slightly but significantly increased at THC concentrations between 1–2 ng/mL (OR = 1.54, CI = 1.09–2.2) in whole blood. At THC concentrations > 2 ng (in whole blood) crash increased to 2.1. Based on these data, the authors concluded that driving under the influence of cannabis increases the risk of becoming involved in a crash. It should be noted however that the THC ranges given in the Laumon study are not fully complementary and that OR for concentrations between 2–3 and 4–5 ng/mL were not given.

Case-control studies

Several epidemiological studies have attempted to include a representative control group to calculate risk ratios for traffic related hospitalization after THC use. Hingson et al. [32] conducted an anonymous random telephone survey of nearly 6000 16–19 year olds which indicated that frequency of driving after cannabis use was associated with greater accident involvement in the year prior to the interview. Compared to subjects who did not drive after cannabis use, subjects who drove after smoking marihuana on at least six occasions/month were 2.4 (95% CI: 1.4–14) times more likely to be involved in traffic accidents. Those who drove after marihuana use on at least 15 occasions/month were 2.9 (95% CI: 1.3–6.8) times more likely to have an accident.

Mura et al. [33] conducted a case-control study to compare the prevalence of THC among injured drivers and control subjects that were recruited from emergency departments in six French hospitals. Total study population comprised 900 drivers involved in a non-fatal accident and 900 control drivers who attended the same emergency units for non-traumatic reasons. Drivers and controls were matched for sex and age. THC (> 1 ng/mL whole blood, no other drugs or alcohol present) was detected in 10% of the injured drivers and in 5% of the controls when averaged over all age groups. In cases and controls who were younger than 27 years, THC was detected in 15.3% of the cases and 6.7% of the controls, giving rise to an odds ratio (OR) of 2.5 and a 95% CI ranging from 1.5–4.2. In cases where both THC and alcohol (BAC > 0.05 g/dl) were present the OR increased to 4.6 (95% CI: 2.0–10.7).

Gerberich-Goodwin et al. [34] conducted a retrospective study in a large prepaid Northern Californian health care program cohort (N = 64 657) to compare the incidence of traffic injury related hospitalisation among THC users and non-drug users. All cohort members completed baseline questionnaires about health behaviours, including cannabis use between 1979 and 1985. Traffic injury related hospitalisations were identified from the date of baseline through December 1991. An increased risk ratio (OR = 2.3, 95% CI: 1.44–2.72) for motor vehicle injuries was demonstrated in male cannabis users relative to non-users.

Data from these studies clearly suggest that cannabis increases a driver's risk to become involved in a road crash. Yet, it has been argued that such associations may be confounded by life style factors typical for cannabis users. Fergusson and Hor-

wood [35], for example, established a statistically significant relation between self-reported frequency of cannabis use and self reported accidents rate (OR 1.6, 95% CI: 1.2–2.0) in a birth cohort of 907 young New Zealanders (aged 18–21). Adjusting for risky driver behaviors and unsafe driver attitudes characteristic for cannabis users, however, eliminated the association between cannabis use and crash risk. Another example was given by Blows et al. [36] who conducted structured interviews among 571 driver cases involved in crashes and 588 control drivers in New Zealand. They reported a significant relation between self-reported recent (acute) use of cannabis and car crash injury (OR 3.9, 95% CI: 1.2–12.9). However, after adjustment for potential confounders such as seat belt use, sleepiness or speeding the association was no longer significant. These analyses suggest that traffic accident risk among cannabis users is related to their life style rather than to cannabis use *per se*. However, these results may also be taken to support an alternative explanation: i.e. cannabis stimulates risky driving behaviors and/or attitudes that are linked to accident risk [37].

Two studies [38, 39] have employed a prospective case-control study design that has historically been the design of choice for epidemiological studies of the role of alcohol in motor vehicle crashes [40]. Crash risk was evaluated by calculating the odds of an individual in a crash sample testing positive for cannabis to the odds of an individual testing positive for cannabis in the exposure sample, that is, in a roadside survey sample of non-crash-involved drivers using the same roads in the same time frame. In the study by Movig et al. [39], cases (N = 110) were car drivers involved in road crashes in the Tilburg area of the Netherlands, whereas controls (N = 816) were recruited at random from the general driving population on public roads in the same Tilburg region between May 2000 and August 2001. Controls were tested for the presence of cannabis by means of urine sample screening. If no urine sample could be collected a blood sample was requested. In total, 79.3% of the control group was willing to participate in the study. Cases were tested for THC in blood or THC-COOH in urine from samples taken directly in the emergency room. Among cases, 13 (12%) tested positive for cannabis as compared to 49 (6%) among controls. A non-significant increase in risk ratio was reported for cannabis (OR = 1.22, 95% CI: 0.55–2.73) indicating no association between exposure to cannabis and road accidents. The case-control study by Movig et al. [39] was later extended for another three years to increase the number of cases and controls [41]. By the end of this period the complete study set (i.e. data collected from 2000–2004) included 207 cases and 3799 controls. Overall, the number of drivers that refused study participation was rather low, i.e. 1.4% of drivers stopped at the roadside. Analyses of the extended dataset again revealed no significant association between crash risk and cannabis exposure (OR = 1.45, 95% CI: 0.6–3.3). The authors argued that the absence of an association between cannabis use and crash risk might be partly related to an uneven distribution of urine and blood samples in cases and controls. In the majority of cases THC was determined in blood, whereas in the majority of controls THC-COOH was determined in urine. THC use in control drivers thus may have been representative of past use of cannabis rather than recent use as argued above.

Consequently, an overrepresentation of past cannabis use among control drivers use may have led to an underestimation of crash risk following recent cannabis use.

Dussault et al. [38] presented results of a large case-control study comparing the presence of cannabis in crash involved drivers (N = 354) to presence of cannabis in drivers participating in a roadside survey (N = 11 574) between 1999–2001 in Quebec, Canada. The survey sample was distributed proportionally to the number of crashes per time of day (eight 3-h periods) and day of the week (seven days). Cannabis was detected in urine of 19 % of all cases, whereas the same drug was detected in urine or saliva of 6.2 % of controls. Actual participation rate among controls as defined by how many controls were willing to provide a saliva or urine sample was 84.6 %. Case-control analysis suggested that cannabis is associated with twice the risk of being fatally injured in traffic (OR 2.2; CI: 1.5–3.4). Sharp elevations in crash risk were found for combined use of cannabis with alcohol (BAC > 0.08 g/dl; OR 80.5; 95 % CI 28.2–230.2), cocaine (OR 8.0; 95 % CI: 3.1–20.7) and benzodiazepines (OR 21.3; 95 % CI: 5.3–86.0). Remarkably, a culpability analysis of all cases did not reveal a significant rise in crash risk in cannabis users, indicating that this type of analyses may be less conclusive.

Experimental studies of cannabis and performance

Determination of the effect of THC on performance has mostly been based on information provided by the field of psychopharmacology. Psychopharmacologists have devised a large number of "psychomotor" tests, characterized by contingent motor responding to an imposed discrete or continuous signal (e.g. reaction time, attention, tracking and critical flicker/fusion frequency tests), and "cognitive" tests for measuring various mnemonic functions but also deductive reasoning. Finally, tests were developed to measure some aspects of "real life" performance such as driving in a simulator, through staged maneuvers on a course closed to other traffic or on public roads in actual traffic. Experimental studies have followed both parallel group and crossover designs, most with both placebo- and alcohol controls. The great advantage of experimental studies that have been conducted is their ability to determine the intrinsic pharmacological effects of THC on performance without the confounding factors that always obscure or exaggerate the effect in the natural environment. However, until now the experimental approach has been mostly limited to studies assessing the acute effects of THC on performance, i.e. the effects of THC on performance after a single dose. Experimental data on performance effects after repeated doses of THC is generally lacking. As a consequence it is currently not known whether THC users adapt to acute effects of this drug as a result of tolerance. Neither have the effects of THC been systematically studied in novel users *vs*. experienced users to establish differences in sensitivity between subgroups of users. These issues will certainly gain importance with the possible introduction of cannabis as a medicinal drug for the (sub)chronic treatment of pain or inflammation. It is for this reason that the Institute of Medicine, Washington DC, advises to

assess the cognitive and psychomotor functioning before and regularly during the course of a chronic regimen of cannabis treatment to determine the extent to which tolerance to the impairing effects of cannabis develops and whether new problems develop [42].

Psychomotor performance and cognition

Numerous experimental studies have been conducted to investigate the effects of THC on isolated cognitive functions and psychomotor skills related to driving performance. These have generally shown that THC in doses between 40 and 300 μg/kg causes a dose dependant reduction in performance at laboratory tasks measuring memory function, divided and sustained attention, reaction time, tracking or motor control [1, 2, 5, 6, 43–45]. One of the most consistently reported behavioral effects of THC is a disruption in the free recall of previously learned information. Recall of items learned before cannabis use is generally not affected, suggesting that THC impairs learning and the acquisition of information but not its retrieval from memory. Short-term or working memory is generally impaired in complex tasks, but at high doses also in simple tasks.

The magnitude of the THC effects on performance furthermore varied with the application form, i.e. smoking or oral intake, and time post THC use. Berghaus et al. [2] conducted a meta-analysis in 87 studies on the effects of THC on psychomotor function, including tracking, reaction time performance, perception, eye-hand coordination, body sway, signal detection, divided or sustained attention tasks. Their analysis demonstrated that the percentage of psychomotor tasks showing significant performance impairment after THC was highest during the 1st hour after smoking or between 1–2 hrs after oral intake. Peak impairment after THC was comparable to alcohol induced performance impairment seen at blood alcohol concentrations (BACs) > 0.05 g/dl. The number of significant performance effects sharply declined to about zero over 3–4 hrs after THC use. Only higher doses of THC produced prolonged performance impairment. The authors also established a concentration-effect curve, which indicated that, at least for low concentrations, plasma concentrations of THC are approximately linearly related to the magnitude of performance impairment. This relation was almost identical in experiments with smoking compared to experiments with oral intake of cannabis. In general, performance declined in about 35 % of all tests applied at plasma concentrations of about 5 ng/mL THC, when compared to placebo. Impairment increased with higher plasma levels of THC. Maximal performance decrement, i.e. impairment in 70–80 % of all psychomotor tests, was seen at concentrations between 14 ng/mL and 60 ng/mL THC. The THC concentration effect curve was based on all experimental tests included in the meta-analysis. The majority of these experimental tests were conducted between 15 min and 4 h after drug intake. THC concentrations were estimated from dose and time of testing by means of pharmacokinetic modelling [42]. A summary of the major findings from the Berghaus et al. meta-analysis is given in Table 2 and Figure 1.

Table 2 Frequency of performance impairments (%) observed in the total number of psychomotor tests applied in 87 experimental studies as a function of dose, time after dosing and route of administration of THC. Performance decrements associated with less than 20 psychomotor assessments are put in brackets because of their limited predictive validity (Adapted from: Berghaus et al., 1998a).

Time after smoking (h)										
THC-dose	**<1**		**1–2**		**2–3**		**3–4**		**4–5**	
	Impaired	**# Tests**	**Impaired**	**# Tests**	**Impaired**	**#Tests**	**Impaired**	**# Tests**	**Impaired**	**# Tests**
Route of THC administration: smoking										
<9 mg	61%	271	36%	33	(30%)	10	(0%)	10	(0%)	11
9–18 mg	53%	193	38%	48	(38%)	8	(0%)	6	(0%)	2
≥18 mg	64%	64	36%	28	(40%)	10	(53%)	15	(67%)	3
Overall	**58%**	**528**	**37%**	**109**	**36%**	**28**	**26%**	**31**	**(13%)**	**16**
Route of THC administration: oral										
<9 mg	(33%)	3	14%	49	27%	37	(8%)	13	-	-
9–18 mg	(0%)	3	39%	41	42%	45	(18%)	17	-	-
≥18 mg	(0%)	3	60%	45	(40%)	15	(33%)	15	(45%)	11
Overall	**(11%)**	**9**	**37%**	**135**	**36%**	**97**	**20%**	**45**	**(45%)**	**11**

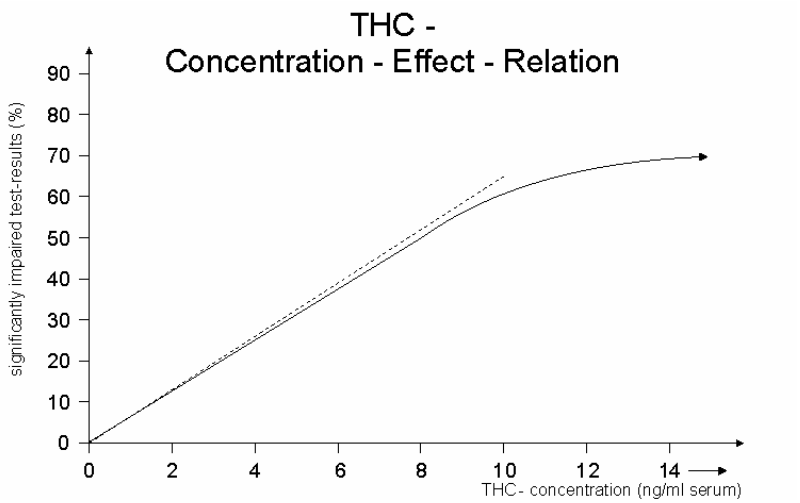

Figure 1 Frequency of performance decrements (%) observed in the total number of psychomotor tests applied in 87 experimental studies as a function of THC concentration in plasma after eating (---) and smoking (—) cannabis (Adapted from Berghaus et al., 1998a).

Driving simulators and on-the-road driving tests.

A potential disadvantage of experimental laboratory studies is that it is often unknown whether tests of skills related to driving serve as a good model for the driving task as a whole. Many tests are short and relatively simple and do not necessarily reflect performance in the real world. Driving is probably one of the most complex psychomotor tasks. It is difficult to conceive, much less simulate, every situation that confronts drivers. Tests for measuring effects of drugs in driving simulators, over closed-course driving terrain or on real roads in normal traffic are most likely to approach reality. Yet, these tests also can often measure only parts of the total driving behavior. However, it is generally accepted that the closer a test approaches reality, the better the chance of measuring effects that cause crashes.

Studies in interactive driving simulators [47–50] showed that THC doses up to 200 μg/kg increased lateral position variability, headway variability and caused subjects to ignore navigational information. The highest dose increased speed variability and caused the subjects to hit roadway obstacles more often and to react more slowly to subsidiary task demands. Yet THC also caused subjects to drive in a more conservative manner. They maintained a longer headway, refused more opportunities to pass and, when they did, began this maneuver at greater distance from the approaching vehicle. However, this compensatory behavior was never sufficient to fully overcome the overall impairing effect of cannabis. Studies designed to test the effects of THC on vehicle handling performance during staged maneuvers on terrain closed to traffic generally failed to show any dramatic changes in performance [51–53]. However, THC doses and number of subjects in these studies

were generally too low to achieve sufficient statistical power to detect any drug effect on performance.

Klonoff [54] was the first to conduct a driving test in actual traffic. A total of 38 subjects were divided over separate groups to receive placebo, THC 4.9 mg or 8.4 mg. After smoking, subjects drove for 45 minutes on city streets of Vancouver while aspects of their performance were rated by a professional examiner from the State Department of Motor Vehicles. No evidence was given of the reliability of these subjective judgments, and this may have been the source of the large variability found in performance after cannabis. Out of 11 scales of subjective judgments that were used in this study only three seemed to be significantly affected following the highest dose: concentration, care while driving and judgment.

The most comprehensive series of driving tests in actual traffic were conducted by a group of researchers at Maastricht University, The Netherlands. Robbe [1, 55] investigated the effects of THC 0, 100, 200 and 300 µg/kg on performance in a one-hour Road Tracking Test and a 30-minute Car-Following Test conducted on a primary highway, as well as the effects of alcohol and THC 100 µg/kg on performance in a City Driving Test. The combined effects of THC and alcohol on performance in the same tests were further investigated in subsequent studies [55–57]. All subjects were recreational users of cannabis. THC produced a dose related increment in the Standard Deviation of Lateral Position (SDLP), a measure of lateral position variability or "weaving", during the Road Tracking Test. Reaction time to speed accelerations/decelerations of a leading vehicle and general driving proficiency were not affected by THC in the Car-Following Test and the City Driving Test respectively. The effects of THC on lateral position variability were moderate and comparable to

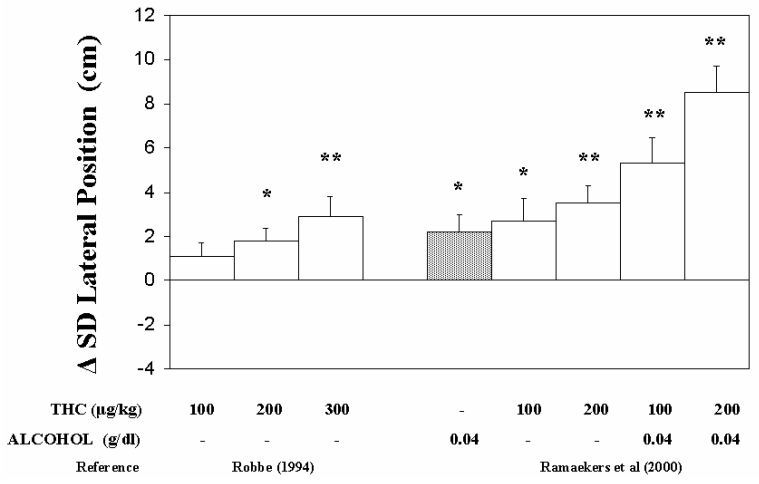

Figure 2 Mean Δ SDLP (+SE) in the Road Tracking Test after incremental doses of THC alone and after THC combined with alcohol as measured in studies by Robbe (1994) and Ramaekers et al. (2000) respectively. Alcohol concentrations reflect the subjects' mean BACs while conducting the driving test. Significance of changes in SDLP is indicated as follows: * $p < 0.05$; ** $p < 0.01$. Mean (range) plasma THC concentrations after 100, 200 and 300 µg/kg were 7.9 (0.8–17.2), 12.0 (1.5–27.1) and 16.1 (4.7–30.9) ng/mL (Robbe, 1994).

that of an alcohol dose producing a BAC of about 0.05 g/dl, the legal limit for driving under the influence in most European countries. However, its combination with a low dose of alcohol (i.e. BAC < 0.05 g/dl) produced severe performance impairment in the Road Tracking Test, and to lesser extents also in the Car-Following and City Driving Test. There was no significant interaction between alcohol and THC, indicating that the effects were additive. When compared to a previously established alcohol calibration curve [58], the combination of THC 100 and 200 µg/kg with alcohol produced a rise in mean SDLP the equivalent of that associated with BACs of 0.09 g/dl and 0.14 g/dl, respectively. A summary of the effects of THC and alcohol on lateral position variability is given in Figure 2. Values on the Y-axis indicate change scores from placebo.

Predictive validity of experimental performance tests

The predictive validity of performance tests in drugs and driving research is usually unknown, primarily due to a lack of real-life epidemiological (crash risk) data in general. The absence of such data has made attempts to correlate laboratory data to real life driving accidents extremely difficult. In addition, both experimental and culpability studies have neglected to describe driver impairment or crash risk as a function of THC concentration in blood. Recently, these issues were overcome by researchers in the fields of psychopharmacology and forensic toxicology who undertook experimental [59] and culpability studies [30] to assess THC induced driver impairment in laboratory performance tests and THC induced crash risk in real-life as a function of THC concentration in blood. The experimental and culpability studies were mutually supportive and, for the first time, demonstrated a gradual increase in performance impairment and crash risk with rising THC concentrations in blood.

A description of the Laumon study has previously been given under section 2.2. The experimental performance study by Ramaekers et al. [59] involved 20 recreational users of cannabis who participated in a double-blind, placebo controlled, three-way cross-over study. Subjects were administered single doses of 0, 250 and 500 µg/kg THC by smoked route. Performance tests measuring skills related to driving were conducted at regular intervals between 15 min and 6 h post smoking and included measures of perceptual-motor control (Critical Tracking Task), motor impulse control (Stop Signal Task) and cognitive function (Tower of London). Blood was collected throughout testing. Individual THC concentrations in serum prior to performance assessments in each of the THC conditions were divided over six mutually exclusive categories covering the full range of THC concentrations. Corresponding change scores, i.e. performance scores during THC treatment minus performance scores during placebo treatment, of task performance were then classified either as showing “impairment” or “no impairment” for all individual cases within each of the THC concentration categories. Results showed that the

proportion of observations showing impairment progressively increased as a function of serum THC in every performance task.

The THC concentration-effect curves for culpability risk [30] and performance impairment [59] are given in Figure 3. It shows a remarkable correspondence between THC induced impairments in three performance tasks and THC induced culpability risk. It should be noted that THC concentration in the original publications by Ramaekers et al. [59] and Laumon et al. [30] were given as serum and whole blood values respectively. In order to increase comparability, whole blood values were divided by two in order to obtain equivalent serum concentrations [60]. Paired means of performance impairments in each of the experimental tasks and culpability risk within five serum THC concentration ranges (i.e. 0–1, 1–2, 2–5, 5–10 and >10 ng/mL) were taken as input for curve estimation and correlation analyses. It was assumed that these THC ranges would represent the THC ranges presented in both studies, even though THC concentrations between 2–3 and 4–5 ng/mL were not presented or were missing in the Laumon study. The analyses showed that data pairs of performance impairment and culpability risk can be perfectly fitted in exponential curves for performance tests measuring tracking performance, impulse control and cognitive function. In addition, THC induced performance impairments and THC induced culpability risks were highly correlated (see Fig. 4). The implication is that these performance tests of skills related to driving can be taken as valid measures to predict THC induced crash risk in real life.

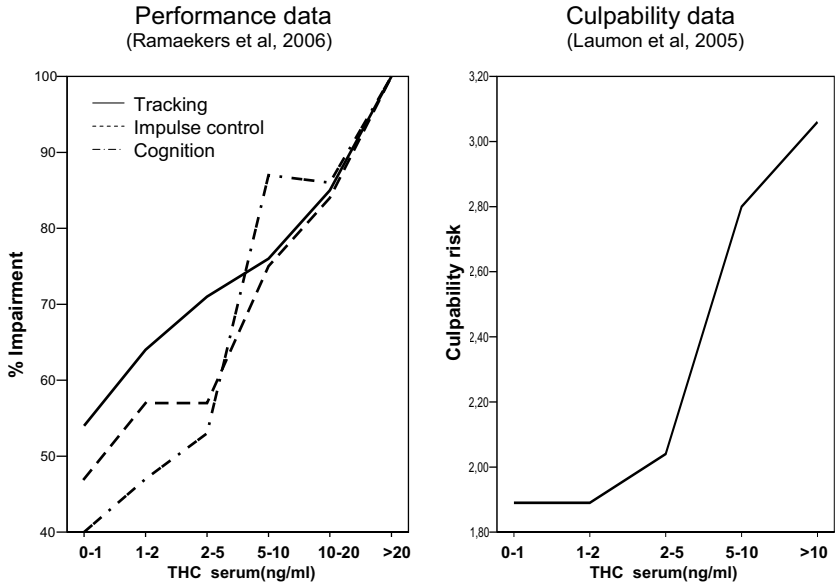

Figure 3 The left panel shows mean performance impairments (% of cases) observed in the Critical Tracking Task (tracking), Stop Signal Task (impulse control) and the Tower of London task (cognition) as a function of serum THC. The right panel shows mean crash risk as a function of serum THC.

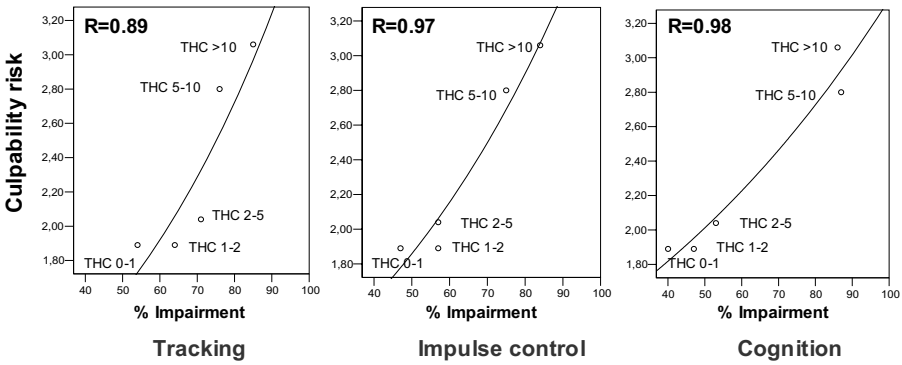

Figure 4 THC (ng/mL) induced culpability risk as a function of THC (ng/mL) induced performance impairment observed in the Critical Tracking Task (tracking), Stop Signal Task (impulse control) and the Tower of London task (cognition).

THC limits of impairment

many jurisdictions in countries worldwide are adopting laws to address the traffic safety problem caused by drugged driving. Many of these laws are designed as *per se* laws with a zero tolerance for major illicit drugs. Such "zero-tolerance" laws are already in place in several U.S. states and in European countries. Yet, there is little scientific evidence to show that detection of THC or THC-COOH in bodily fluids can be taken as proof of impairment in any circumstance. Recently, an international working panel of physicians, forensic toxicologists and psychologists was assembled to elaborate and offer recommendations for the development of a rational legal framework on driving under the influence of cannabis [61]. It reviewed scientific evidence from experimental and epidemiological studies on the impairment of drivers by cannabis. The working panel concluded that a rational limit for relative impairment by THC was likely to be found in the 5–10 ng/mL serum range. That conclusion was primarily based on a meta-analysis of experimental data that suggested that THC concentrations in serum of 4 to 10 ng/mL are associated with the same overall rate of performance impairment as BACs of 0.04 to 0.08 mg/ml [2] and on the culpabity data by Drummer et al. [29] that showed elevated crash risk for serum THC concentration > 10 ng/mL (i.e 5 ng/mL in whole blood).

Since the recommendation by Grothenhermen et al. [61], three studies have been conducted that have specifically addressed the relationship between THC concentrations in blood and driver impairment [30, 59, 62]. Khiabani et al. [62] performed clinical tests for impairment in 456 apprehended drivers who tested positive for THC in whole blood. In total, 54 % of the drivers was judged not impaired by a police physician and 46 % was considered impaired. Impaired drivers demonstrated higher median THC levels (2.5 ng/mL, range 0.3–45.3 ng/mL) as compared to non-impaired drivers (1.9 ng/mL, range 0.32–24.8) but the concentration ranges in both groups were widely overlapping. The percentage of drivers judged impaired

increased from 38% at low THC concentrations (THC <1 ng/mL) to 57% at the highest THC concentration (THC >10 ng/mL). Drivers had an increased risk for being judged impaired at THC levels >3 ng/mL in whole blood (i.e. approximately 6 ng/mL in serum). The studies by Ramaekers [59] and Laumon [30] have been discussed above (see also Fig. 3). The former concluded that performance impairment selectively emerged at serum THC concentrations between 2–5 ng/mL and became truly prominent across all performance domains at serum THC concentrations between 5–10 ng/mL. The latter demonstrated significant increments in crash risk drivers with THC concentrations >2 ng/mL in whole blood (i.e. approximately 4 ng/mL in serum), when adjusted for all confounders.

Discussion

The epidemiological literature has provided conflicting information on the role of THC in performance impairment and motor vehicle crashes. Among epidemiological studies, case-control studies are limited in number but generally provide evidence supporting an association between cannabis and increased crash risk. The majority of epidemiological studies are culpability studies and several of these show little evidence that drivers who only used cannabis are more likely to cause accidents than drug free drivers. In contrast, experimental studies have convincingly and repeatedly demonstrated that THC in doses up to 300 μg/kg causes impairment of various cognitive and psychomotor functions and of driving performance as measured in driving simulators or on-the-road tests. The magnitude of these performance impairments were comparable to alcohol induced performance impairment seen at BACs ≥0.05 g/dl, and should be considered as practically relevant. The reason for the apparent discrepancy between experimental and culpability studies is largely unknown but may be related to inadequate attribution of cannabis use to crashed drivers. These frequently relied on the detection of an inactive metabolite of THC in urine of drivers to establish the use of cannabis. However this metabolite, THC-COOH, can be assessed in body fluids for hours and days and is not a reliable indication of recent cannabis use or impairment. Recent exposure to cannabis can only be safely assumed in the minority of culpability studies that determined cannabis use by the presence of THC in the blood. This latter procedure was only followed in three surveys. In these studies, culpability odds ratios in THC positives were generally higher than those in THC-COOH positives. Moreover, culpability odds ratios in THC positives were 2–7 times as high as compared to drug free drivers, depending on the concentration of the drug detected in blood. Together, these data indicate that recent cannabis use may increase crash risk, whereas past use of cannabis as determined by the presence of THC-COOH in drivers does not.

There are more general limitations to culpability studies that should be considered as well. The analysis assumes that drug free drivers involved in crashes are representative for the driving population at large. If so, culpability odds ratios may well establish reliable estimates of odds ratios that would be obtained in case-con-

trol studies using non crash drivers from the general driving population as control. However this may not always be the case. Bates and Blakely [4] pointed out that outcome misclassification may introduce bias. Determination of culpability status is not exact and there may be a tendency to misclassify drivers who are in fact responsible for the accident as not, or vice versa. However, it is noteworthy that studies that established cannabis use by measuring THC in blood [26, 29, 30] all used an identical method for establishing driver culpability. The fact that one of these surveys reported increased culpability rates in injured drivers therefore most likely reflects the large THC concentrations found in these particular crash victims and not a structural difference in outcome classification between studies.

Bias may also occur if the control group of drug free cases is not controlled for confounding factors. Confounding could occur if there are lifestyle factors associated with cannabis use that are also independent risk factors for traffic crashes such as age, sex, time of accident or the use of alcohol. Confounding by alcohol is always avoided in culpability studies by excluding cases with alcohol present in their blood from statistical analyses of risk associated with cannabis. However, the potential role of other confounders is generally not taken in consideration. The possibility therefore exists that culpability studies identify an elevated risk of dying in road accidents if one is young, male and driving on weekends, instead of an elevated crash risk after recent use of THC as suggested. However, this is not likely to be the case in the two culpability studies so far that showed elevated crash risk in THC positive drivers. Drummer et al. [29] and Laumon et al. [30] adjusted for potential confounders such as age, sex, crash type, jurisdiction and year of collection in their analysis, which provided extra support to their notion that the rise in culpability ratio was caused by cannabis and not by some other factor.

Recent epidemiological studies of the relation between cannabis and motor vehicle crashes have also involved a number of case control designs. The majority of these studies have suggested that cannabis is associated with twice the risk of becoming involved in traffic accidents. Two case-control studies seem of particular interest because they have used the classic study procedures that have previously been validated for alcohol in the Grand Rapids study [40]. Basically, these studies have compared the prevalence of cannabis use among crashed drivers to the prevalence of cannabis among the drivers who were passing the same roads in same time period. This approach is generally accepted as a very reliable and solid method for establishing drug related crash risk. Epidemiologists have however long refrained from conducting such studies in cannabis research because of the participation problem. That is, identification of cannabis would require a blood sample from control drivers on a voluntary basis. Because cannabis is an illegal drug it is likely that drug users would be less willing to participate in the study than non-drug users. This would potentially bias study results and inflate odds ratios. Possible alternatives to blood sampling would be to collect non-invasive matrices such as urine and saliva as applied in the studies by Dussault et al. [38] and Movig et al. [39]. In both studies the response rates among controls were reasonably high, i.e. around 80–85 %, which indicates that most controls are willing to cooperate in roadside drugs testing. Though not optimal, these numbers should increase confidence in the

feasibility of case control designs for establishing the relation between cannabis and crash risk.

Experimental and epidemiological research converges on the fact that the association between THC and driver impairment is dose related. Odds ratios for accident culpability were shown to increase with increasing concentrations of THC in the blood of (fatally) injured drivers. Likewise, performance impairments in psychomotor or cognitive tests and lateral position variability in experimental driving tests were shown to gradually increase with increasing doses of THC. This may prove relevant since it has been argued that most THC doses employed in experimental research have been less than those used for recreational purposes in real-life. In a dose finding study by Robbe [1] 23 subjects who were all recreational users of THC indicated that they had achieved their desired psychological effect after smoking a mean dose of 300 μg/kg (i.e. identical to smoking about 20 mg THC by a person of average weight). The range of this preferred dose varied between 194–524 μg/kg THC indicating considerable inter-individual variation. It is thus likely that drivers in the general population will at times use doses that are higher than the ones used in experimental studies or associated with average concentrations detected in epidemiological surveys. It has recently been shown that the use of higher doses (i.e. >300 μg/kg THC) will be associated with severe driving impairment, equivalent to BACs >0.08 g/dl [59, 63].

The clear dose/concentration-effect relation between cannabis use and driver impairment or crash risk raises the question whether a "*per se*" limit could be identified above which drivers are always at risk. Current implications of experimental and epidemiological data seem twofold. First, it is evident that no performance impairment or crash risk is associated with serum THC concentrations <2 ng/mL (i.e. 1 ng/mL in whole blood). In terms of driving under the influence of cannabis this may be of particular importance in relation to residual serum THC concentrations of 0–2 ng/mL that can be found in frequent THC users [60] or even in non-users who have been passively exposed to cannabis. Second, experimental and epidemiological data also indicate that any scientific THC limits should be in the range of 2–10 ng/mL in serum (i.e. 1–5 ng/mL in whole blood). Experimental data indicate that impairment emerges at serum THC concentrations >2 ng/mL, whereas epidemiological data indicates that crash risk emerges at serum THC concentrations between 4–10 ng/mL. It should be stressed however that the predictive validity of any *per se* limit is confined to the driving population at large, and not necessarily applicable to each and every driver as an individual. Individual drivers can widely differ in their sensitivity for THC induced impairment as evinced by the weak correlations between THC in serum and magnitude of performance impairment [59].

It is also absolutely clear from epidemiological and experimental studies that the combination of alcohol and THC plays a major role in performance impairment and motor vehicle crashes. The epidemiological evidence shows that the combination of alcohol and THC is over-represented in injured and dead drivers, and particular in those responsible for the accident to occur. Experimental studies have shown that alcohol and THC combined can produce severe performance impairment even when given at low doses. The combined effect of alcohol and cannabis on perfor-

mance and crash risk appeared additive in nature, i.e. the effects of alcohol and cannabis combined were always comparable to the sum of the effects of alcohol and THC when given alone.

Experimental studies furthermore indicate that not all driving tasks are equally sensitive to the detrimental effects of THC. Performance was always worst in tests measuring driving skills at the operational level, i.e. tracking and speed adjustment, as compared to performance in tests measuring driving performance at the maneuvering level, i.e. distance keeping and braking, and the strategic level, i.e. observation and understanding of traffic, risk assessment and planning. Strategic and maneuvering levels are particularly demanding of resources in that they require effortful processing and attention. Thus processing is relatively slow and flexible. In contrast, the operational level is considered to be an automatic, routine process, which is fast and relatively inflexible. Drivers may be particularly vulnerable to detrimental effects of THC in traffic situations where they specifically employ driving skills that are operated at lower automated levels, such as during highway driving. The implication might be that drivers under the influence of THC might be more likely to be involved in specific types of traffic accidents such as single vehicle crashes. Culpability studies by definition have neglected this possibility, since drivers involved in this type of accident are practically always responsible, irrespective of drug use.

Conclusions

- THC has been shown to impair cognition, psychomotor function, actual driving performance and crash risk in a dose related manner.
- The degrees of impairment observed in laboratory or actual driving tests after doses up to 300 μg/kg THC were comparable to the impairing effects of an alcohol dose producing a BAC $\geq$0.05 g/dl, the legal limit for driving under the influence in most European countries.
- There is no indication that *past use* of THC alone affects crash risks, but there is growing evidence that *recent use* of THC increases the risk for motor vehicle accidents compared to drug free drivers, particularly at higher concentrations.
- Significant performance impairment emerges at serum THC concentrations >2 ng/mL and crash risk significantly increases at serum THC concentrations between 4–10 ng/mL.
- Detrimental effects of THC appear more prominent in highly automated driving behavior, as compared to more complex driving tasks that require conscious control.
- The effects of THC and alcohol on driving performance and risk of motor vehicle crashes appear to be additive, but the sum can be large and potentially dangerous. Combined use of THC and alcohol produces severe driving impairment and sharply increases the risk of drivers' accident culpability as compared to drug free drivers, even at low doses.

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Drugs, Driving and Traffic Safety
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Ecstasy, driving and traffic safety

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Abstract

Ecstasy (methylenedioxymethamphetamine, MDMA) is a synthetic drug which is popular among clubbers who love it for its euphoric and energizing effects. These subjective effects are experienced approximately between one and four hours after intake. It is also shown that MDMA affects driving-related behavior, as measured by performance tasks and simulated driving, as well as actual driving as assessed by on-the-road driving tests. Under optimal conditions that are during daytime, moderate doses, and with no co-use of other substances MDMA exerts stimulating effects on reaction time performance, tracking and weaving. However, when MDMA is combined with alcohol or sleep deprivation, these stimulating effects are no longer observable. Combined use of MDMA with cannabis or alcohol is common among ecstasy users. In addition, they usually take the drug at night and drive in the morning after a night of partying and sleep loss. Experimental data have shown that the stimulating effects of MDMA are not of sufficient magnitude to compensate for the impairing effects of sleep loss. Moreover, subjective data have shown that ecstasy users are not able to accurately estimate their objective impairment when under the influence of MDMA. Their lack of judgment during intoxication can put them at risk when engaged in traffic. Epidemiological studies and case studies have also shown that MDMA at normal doses (75 mg) is able to impair driving performance which is characterized by reckless behavior such as speeding and jumping red traffic lights. In addition, in a number of fatalities, ecstasy was detected in the blood of the driver. In sum, MDMA can exert stimulating effects on some aspects of driving when given at low doses. However MDMA is likely to produce driving impairment in combination with other drugs or during a night of sleep loss as is often the case in regular ecstasy users.

Introduction

Ecstasy (methylenedioxymethamphetamine, MDMA) is a synthetic drug that is commonly used by people in the dance scene [1]. It was in the late eighties that

along with the increasing number of large dance parties, the so-called raves, its use became popular in Europe [2]. Nowadays, these events are called "electronic music dance events" and they are held in clubs with DJs playing electronic music [3, 4]. Although the prevalence of ecstasy use has shown an upward trend since the nineties [5], it seems to be in decline in the last years [3]. However, a 5-year cross-sectional study in the UK has shown that in spite of the declining trend in ecstasy use, the number of heavy users – characterized by using four pills or more per session – has more than doubled over this period [6]. The current use appears to be the same all over the world with the exception of Australia which accounts for the highest prevalence percentages [3, 5].

A recent report about the state of the drug problem in Europe presented estimations of the prevalence of current and life-time ecstasy use in European countries in adults (15–64 years) and young adults (15–24/34 years). According to this report, life-time prevalence ("ever used ecstasy") of adults and young adults is estimated to range between 0.3 and 7.2 %, and 0.4 % and 18.7 %, respectively for both groups. The current ecstasy use is estimated to range between 0.2 and 3.5 %, and 0.3 % and 12 %, respectively for adults and young adults [5]. These numbers show that the (lifetime and current) prevalence of ecstasy use is higher among younger people. To give an impression about the extent of ecstasy use in this population, prevalence percentages of recent drug use of two popular drugs, i.e. cannabis and amphetamine are presented as reference. It appears that the current amphetamine use in young adults ranges between 0.1 and 2.9 %, and the current use of cannabis ranges between 3 and 20 %. These percentages show that "recent use" of ecstasy is lower than that of the most used illegal drug in Europe, cannabis. Despite this fact it can be stated that the volume of ecstasy use in this population is considerable.

Ecstasy use is common practice among clubbers [7]; this was, among other studies [8], demonstrated by a survey study in the Netherlands [9]. Apparently more than half of the interviewed attendees (64 %) at Dutch dance parties consumed ecstasy. The second most used drug was, with 34 % of the sample, the synthetic stimulant amphetamine. Ten percent of the sample stated to refrain from all drug use [9]. When observing patterns of ecstasy use, it is shown that the majority of the dance attendees take one or two pills on an evening. The timing of intake can differ between individuals. Some ecstasy users "stack", i.e. they take several pills simultaneously; others "boost", i.e. they take a second pill when the desired effect is wearing off. A common practice is the combined use of ecstasy with other substances such as cannabis, alcohol, and amphetamines [4, 8, 10–12].

Drug use is also associated with drug-linked risky behaviors such as having unprotected sex, taking too many drugs and drugged driving [4]. Survey studies measuring the prevalence of drugged driving (road-side surveys) and the intention to drive under influence of drugs have shown that the prevalence of driving under influence of (il)licit drugs is substantial. A 2-year long road-side survey in Norway revealed that 2 % of the 9013 controlled drivers suspected of driving under the influence of drugs (not alcohol) tested positive for MDMA in blood. Of them, 98 % had used multiple drugs; 91 % had used illegal drugs, 7 % medicinal drugs. The most frequently detected illegal drugs were amphetamine and THC. The median age of this group was 24 years [13]. As MDMA use is standard among clubbers [7], it is to

be expected that drugged driving will occur frequently in this population. A survey among Scottish dance attendees affirmed this assumption as more than one third of the sample indicated that they drive when drugged [8]. A second study among Scottish clubbers a few years later revealed that 19% of the sample had driven under influence of drugs during the past year [4]. Australian clubbers did worse as almost half of a large sample indicated on a survey that they "had driven a motor vehicle within four hours of consuming an illicit substance at least once in the past year"; 47% of them had done it several times. The largest part drove after consuming cannabis (46%), followed by ecstasy (33%) and speed (20%) [14]. These subjective data were quantified in another survey study among party attendees in the States. This study revealed that 62% of the sample who indicated that they would drive home after the party was positive for drugs or alcohol when leaving the party [3].

Logan and Couper [15, 16] demonstrated that even "normal" doses of MDMA can cause driver impairment as the MDMA blood plasma levels of a number of impaired drivers was comparable with the plasma levels of recreational users. Case studies give an indication that concern is justified as they have shown that people under the influence of ecstasy display bizarre behavior as demonstrated by speeding and ignoring red traffic lights [17] and uncontrolled lane changing [18]. Epidemiological studies have revealed the involvement of illicit drugs in combination with alcohol in a small percentage (4%) of fatalities [19]. Moreover, in an Australian multi-center case-control study it was established that drivers testing positive for psychoactive drugs were more likely to be culpable for fatalities than drug-free drivers [20].

Behavioral effects of ecstasy

Ecstasy is a synthetic drug and its major psychoactive constituent is ± 3,4-*m*ethylene*d*ioxy*m*eth*a*mphetamine or short, MDMA. In Europe, 80% of ecstasy pills analyzed in 2005 contained MDMA or a substance related to MDMA such as 3,4-methylenedioxyamphetamine (MDA) [5]. The amount of MDMA in a pill was shown to vary between 30 and 80 mg in most of the European countries [5]. Pharmacokinetic data have shown that peak plasma concentrations are reached approximately 2 hours after intake. The subjective effects (energy, euphoria and empathy) begin around 90 minutes after intake and can last up to 4–6 hours [21, 22].

An important question in the light of traffic safety is how the effects of ecstasy on driving performance can be quantified. Subjects' performance under influence of drugs can be quantified in studies with a varying degree of experimental control. In the first category, the naturalistic/quasi-experimental or *uncontrolled* studies, performance is studied a couple of hours after subjects have self-administered the drug. A basic problem of this type of studies is that the exact relation between the drug of interest (MDMA) and the performance effect can not be established because of confounding factors. Some examples of such confounders are the ignorance about the exact dose of MDMA in a tablet, the co-use of other drugs, not measuring the effects at peak blood concentrations and lack of a suitable control group. These

methodological flaws complicate the possibility of finding a cause-effect relation between current ecstasy use and certain adverse behavior, e.g. disturbed impulse control, and impaired actual driving performance. The second category encompasses the experimental placebo-controlled (within subject) studies. The advantage of these controlled studies is that the study drug and dose are known, effects can be studied at peak concentrations and it can be assured that the observed effects are due to the intervention/study drug and not other confounding factors.

A second issue is how to make driving performance operational in an experimental setting. This is difficult since driving is a very complex multi-component task. According to a model of Janssen (1979) driving can be sub-divided into three hierarchically organized levels depending on the demands put on the driver [25]. On the highest, strategic level, trip planning, route selection and risk assessment are defined. On the tactical level, maneuver control is exercised by the driver – negotiating with traffic signs, other traffic participants, obstacles, keeping following distance, changing traffic lanes, overtaking. At the lowest, operational level, also called the control level, automatic action patterns such as maintenance of lane position and adjustment speed are carried out by the driver. The processes at the three levels differ in speed and flexibility with the operations at lowest level being the fastest and most inflexible and operations at the highest level the slowest and most flexible [23–25]. In order to understand the implications of driving under influence of drugs, and in this case MDMA, it is important to study all these aspects of the driving task separately. The tests addressing these various components of the driving task together with the results are discussed below.

Driving-related performance: implementation of the driving task in the laboratory

In recent years, various computer tasks assessing executive, psychomotor and visuo-motor skills and attention have been used to map the effects of MDMA on driving-related performance. In the following paragraph results showing relevance to the driving task will be discussed. The results reflect MDMA effects at T_{max}, i.e. at 1–2 hours after administration unless stated otherwise. The number behind MDMA is an indication of the dose in milligrams, e.g. MDMA-75 means that the administered dose was 75 mg of MDMA. Each task is accompanied by an indication of the performance level i.e.: L1, L2 and L3 respectively depicting the automated, tactical and strategical level.

Performance tasks measuring driving-related skills

Several studies have assessed the effects of MDMA on eye-hand coordination by means of a simple tracking task (L1) [26–28]. Lamers and colleagues' study [26] was the first one to address this type of psychomotor performance and showed performance improved after MDMA-75. This stimulant effect was not replicated in two other studies that found no effects of MDMA-75 and MDMA-100 on track-

ing performance [27] and impairment after repeated MDMA dosing, i.e. 4 hours separating two doses of MDMA (MDMA-75 + 50) [28]. However, this latter study was performed during evening and nighttime hours instead of during the usual daytime hours. The time of day could perhaps have caused this switch in effects from stimulation to impairment. Results on a more complex tracking task (L1 + L2) were univocal, i.e. both studies that used this task found improvement of tracking performance under double task conditions [26, 28] (see Fig. 1a). After a night without sleep, the stimulating effect of nocturnal MDMA-75 + 50 doses on tracking performance was not strong enough to compensate for the lack of sleep and the effect disappeared (see Fig. 1b). Results on the secondary task (visual search: L2) revealed no effects of MDMA-75 on daytime performance [26] but deterioration of target detections, i.e. less detections and slower, during the evening and in the morning after a night without sleep (MDMA-75 + 50) [28]. In concordance with this, Parrott and Lasky (1998) [31] (quasi-experimental study; between 1.45 and 1.8 ecstasy tablets) found some impairing effects on a visual search task. They measured between 2–8 hours and 8–16 hours post-drug at a club venue so it is evident that subjects were lacking sleep and the observed effects were the combination of MDMA and sleep restriction [29]. Risk assessment as measured by time to collision estimation (L3) in a divided attention task was impaired by MDMA-75 [26]. Absence of the impairing effect on this measure was later shown for two doses i.e. MDMA-75 and MDMA-100 in another study [27]. It has to be mentioned however that this was a less complex version than the one used by Lamers and colleagues [26]. Object location identification (L2) in a spatial memory task was shown to be impaired after MDMA-75 and MDMA-75 + 50 repeated dosing. Reaction time (L2) in this task improved under influence of MDMA-75 and MDMA-75 + 50. The impaired localization was not related to the increase in motor speed as shown by a regression analysis [28, 30]. Moreover, in one study these regression results were supported by the fact that the memory impairment was present during the night and after a night without sleep; whereas the improvement of motor speed disappeared in the morning (MDMA-75 + 50) [28]. This dissociation of effects proved that the changes in reaction speed were not the underlying cause of the increased inaccuracy. Movement time (L2) in a choice reaction paradigm was shown to be improved after MDMA-75 [26]. Delayed matching to sample task performance (L1) was not affected by MDMA-75. In this task subjects had to detect whether two successively presented pictures of a traffic situation were identical or differed at some point. This task actually simulates what would happen when you eye-blinked, i.e. whether you would be able to detect a change in a traffic scene. Apparently, subjects under influence of MDMA appear to be as accurate in detecting differences as compared with placebo [30]. Two executive functions tasks, i.e. Tower of London and the Stroop task, assessing planning and mental flexibility (L3) were not affected by MDMA-75 [26] and MDMA-1.7 mg/kg [32]. To assess whether subjects under influence of MDMA accepted higher risks to gain certain fictive rewards, decision-making tasks (L3) (Iowa gambling task and Discounting task) were incorporated in some studies [28, 33]. An absence of effects was shown for several doses of MDMA, i.e. 75, 100 and 75 + 50 mg. The major flaw however with this kind of tests is the fictive nature of the rewards. This is perhaps not the best way to study risk behavior. Downing

(1986) did however find some effects on decision making. In their quasi-experimental study, almost half of the subject sample (4 out of 10), under influence of a self-selected dose of MDMA (range between 1.76 and 4.18 mg/kg; average: 2.51 mg/kg), gave odd responses on hypothetical problems. They therefore advised to

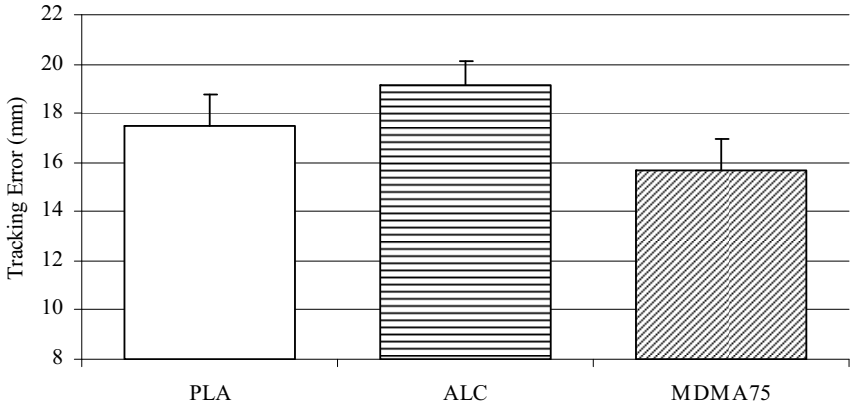

Figure 1a During daytime performance, MDMA (75 mg) improved tracking performance on a divided attention task as indicated by a decrease in tracking error (TE) compared to placebo and alcohol. PLA = placebo, ALC = alcohol, MDMA75 = 75 mg MDMA.

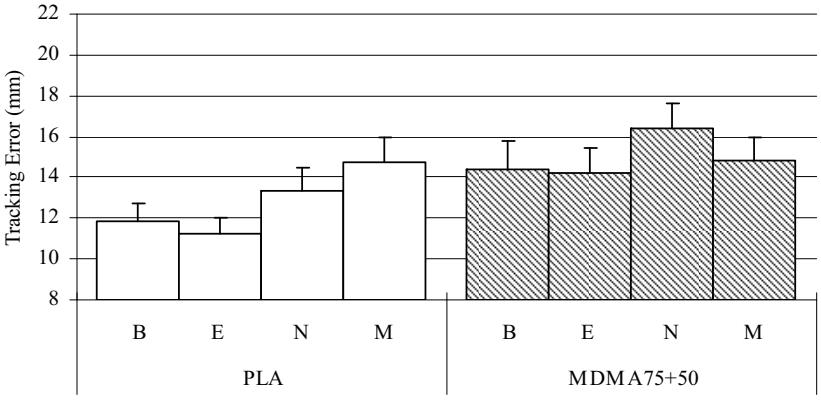

Figure 1b During placebo treatment, performance on the divided attention task deteriorated during the evening and night as indicated by an increasing tracking error (TE). During MDMA treatment, tracking decreased during the night but returned to baseline levels early in the morning. B = Baseline (6.30 p.m.), E = Evening (9.30 p.m.), N = Night (1.30 p.m.), M = Morning (7 a.m.), PLA = Placebo and MDMA 75 + 50 = repeated dosing of MDMA; the first dose (75 mg) was given at 8 p.m., the second dose (50 mg) at 12 p.m.

postpone important decisions in real life until the effects of MDMA have worn off [34]. Besides decision making, another type of risk-related behavior has been assessed, i.e. impulse control. It was shown that MDMA-75 and MDMA-100 exerted a small effect on a stop signal task, i.e. daytime inhibitory control/impulse control

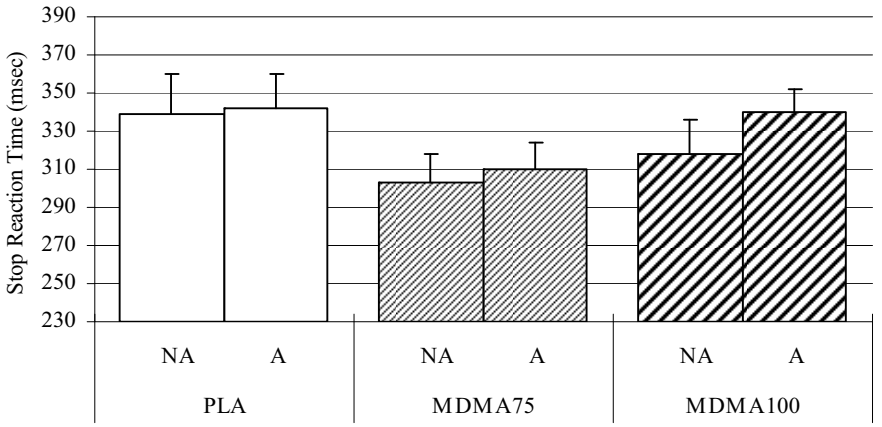

Figure 2a MDMA improved impulse control during daytime as illustrated by the decrease in stop reaction time compared to placebo. NA = no alcohol, A = alcohol, PLA = placebo, MDMA 75 = 75 mg MDMA, MDMA 100 = 100 mg MDMA.

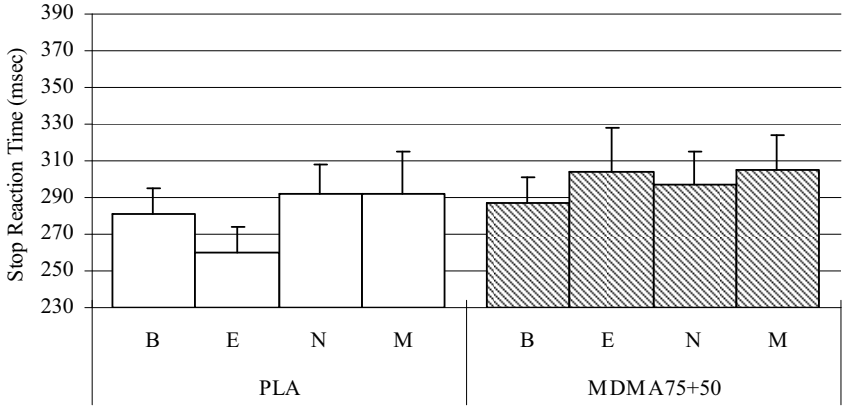

Figure 2b During evening performance MDMA impairs impulse control on a stop signal task as illustrated by the increase in stop reaction time. Nocturnal performance lacks the stimulating effect of MDMA which was present during daytime performance. B = Baseline (6.30 p.m.), E = Evening (9.30 p.m.), N = Night (1.30 a.m.), M = Morning (7 a.m.), PLA = Placebo and MDMA 75 + 50 = repeated dosing of MDMA; the first dose (75 mg) was given at 8 p.m., the second dose (50 mg) at 12 p.m.

improved under influence of MDMA [35] (see Fig. 2a); this stimulating effect on a visual stop sign was absent during the evening and in the morning (after a night without sleep) after repeated nocturnal dosing of MDMA (75 + 50) [28] (see Fig. 2b). In addition, MDMA was not able to counteract the impairing effect of a relatively low dose of alcohol on response inhibition when combined. As this task can be compared with a traffic light turning from green/orange to orange/red, this implicates that a person under influence of MDMA and alcohol would not be able to stop when the color of the lights switches. MDMA-75 and MDMA-100 exerted no effects on performance on a relatively easy short (10 min) continuous performance task [35] (L1). Nighttime performance (5 a.m.) on a longer (45-minutes long) sustained attention task improved after nocturnal doses of MDMA (75 + 50) as was shown by a smaller vigilance decrement after MDMA administration compared with placebo [28]. A working memory task (Digit Symbol Substitution Task) assessing psychomotor speed and memory revealed no effects of MDMA-75 [36] and MDMA-100 [37]. Alcohol alone caused a reduction in performance on this task as exemplified by longer reaction times and less correct substitutions. When combined with MDMA, performance was also reduced, i.e. MDMA was not strong enough to overcome the alcohol-induced impairment; however, the impairment after alcohol lasted longer than when combined [37]. A higher dose of MDMA (125 mg) seemed to impair performance on the DSST as shown by a decrease in total number of correct substitutions and increase in number of errors; there was no effect on reaction time [38]. In a test measuring effects on muscle tension it was shown that MDMA caused muscle tension whereas alcohol was shown to produce muscle relaxation, although non-significant. The combination effects of alcohol and MDMA on the muscles were between the single effects [37, 38].

In general, studies have shown that MDMA improves psychomotor speed/reaction time and psychomotor performance on lower order tests. This was only the case during daytime performance. Higher order processes such as decision making and impulse control were not consistently affected but this could be attributed to the nature of the task. In several tasks it was shown that MDMA was not strong enough to counteract impairing effects of arousal/activation-lowering manipulations such as alcohol or sleep deprivation.

In addition to the objective computer tasks, most studies also used questionnaires to evaluate performance and assess the subjective feelings about the drug effects. Hernandez-Lopez and colleagues [37] reported a discrepancy between subjective and objective measures of sedation or psychomotor impairment. MDMA moderated the subjective experience of alcohol-induced sedation; but it did not compensate for the alcohol-induced impairments on objective measures of psychomotor performance. Whereas objective data seem to indicate that the stimulant effect of MDMA was not sufficient to compensate for the impairing effects of alcohol on psychomotor function and impulse control [33, 37], measurements of subjective impairment have demonstrated that subjects did not notice this impairment. This discrepancy between objective and subjective measures is an issue that deserves extra attention. In real life, subjects tend to rely on subjective feelings to decide whether they find themselves able to drive a car. Subjective measures have clearly shown that subjects are not able to self-judge the extent of their objective impairment. This can be very

dangerous, certainly when subjects have mixed several drugs, are sleep deprived, and want to drive home after a party which is the situation every weekend.

Simulated driving performance

Another way of assessing the effects of drugs on driving-related performance besides using computer tasks that assess aspects of driving performance is by means of a driving simulator test. Brookhuis and colleagues [39] conducted a quasi-experimental/naturalistic study to assess the effects of MDMA and poly-drug use on driving performance in an advanced driving simulator in ecstasy users, before and after visiting a rave party. Participants were people who had self-administered ecstasy (average dose 56 mg) prior to going to a party. Of these, 30–40 % also attested to the concomitant use of alcohol and/or marijuana. When returning from the party, most of the subjects had taken additional doses of MDMA (70 %), marijuana (80 %) or alcohol (90 %). The participants were also tested sober, at a comparable time as the first MDMA ride. The results indicated that driving performance was not greatly affected prior to the rave party, but deteriorated during the night after multiple drug use. A major finding was that lateral and longitudinal control (i.e. automated performance) was not much impaired, but striking was the apparent decreased sense for risk taking (i.e. strategical level), as shown for example by the acceptance of smaller gaps between cars, which increased after MDMA and MDMA in combination with other substances, and sleep loss [39]. These data suggest that combined use of MDMA and alcohol or marijuana produces more severe driving impairment than MDMA alone. However, it should be noted that these data were also confounded by time of testing. Driving impairment was primarily observed when subjects had built up a full night of sleep loss, at the end of the rave. It can thus not be excluded that exhaustion by itself may also have played a major role in driver impairment observed after use of multiple drugs.

On-the-road driving

Computer tasks and a driving simulator test are a good way to study the effects of driving-related performance and/or risk-taking behavior which cannot be conducted in real traffic. A perhaps more valid way to study the effects of drugs on driving performance is to study driving performance on the road. Three standard driving tests were developed to measure each driving performance at another level, i.e. the road tracking test, the car-following test and the city drive which address the operational, tactical and strategical level [40, 41]. To date two studies have been conducted assessing single, residual and combined effects of MDMA with alcohol on actual driving performance, i.e. road tracking and car-following [27, 35]. These data demonstrated that a single dose of MDMA affected automated driving performance, as indicated by a reduction of weaving compared with placebo (measured by the road tracking task). Subjects tended to weave less when under the influence of MDMA. When combined with alcohol, MDMA partially counteracted the impairing effects

of alcohol on weaving (see Fig. 3). Performance on the tactical level (as measured by the car-following task) however was still impaired when alcohol was combined with MDMA. The data suggest that MDMA worsens the impairing effects of alcohol on reaction time performance; however, the interaction term failed to reach significance at the statistical level. In any case, it is clear that MDMA did not reduce the impairing effects of alcohol in the car-following task. This is in line with previous results on a computer task (stop signal task) showing that the stimulant effects of MDMA were not sufficient to overcome alcohol-induced impairment of impulse control or risk-taking behavior [33]. Additionally, a single dose of MDMA seemed to cause an "overshoot" in reactions in the car-following task.

In addition to these objective performance measures, data on subjective feelings have also been collected. In both driving studies, subjects rated the prediction (at the start of the driving test, i.e. 2.5 h post-drug) and evaluation (at the end of the tests, i.e. 4.5 h post-drug) of their driving quality on a ten-centimetre scale. This line represented "very well" at one end of the line to "very bad" at the other end. Subjects also expressed on a scale – after completing the driving tests – the amount of mental effort the driving task required. When under the influence of alcohol, subjects experienced they had to invest more effort when performing the driving tasks. Their subjective experience supported objective measures of alcohol impairments of actual driving. Their impression however that they drove better after intake of MDMA, and had to invest less effort, was only partly reflected in objective measures, i.e. a reduction in standard deviation of lateral position (SDLP). The results from a questionnaire sensitive to subjective effects of several classes of drugs, the Addiction Research Center Inventory (ARCI) showed that MDMA alone produced euphoria and stimulant-like effects. When given in combination

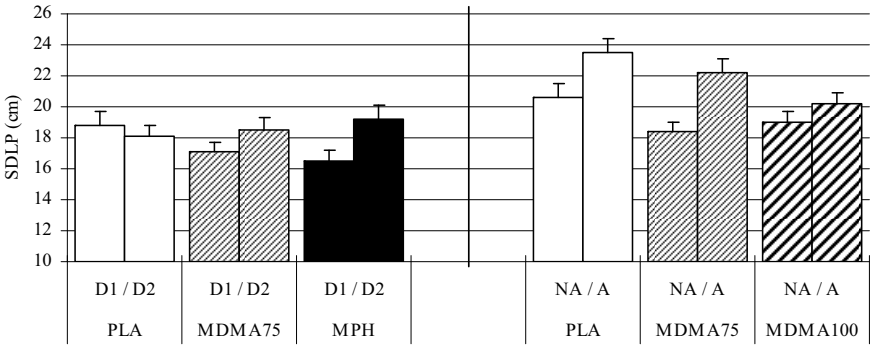

Figure 3 In the left panel, the acute (D1) and withdrawal (D2) effects of a single dose of MDMA on driving performance as measured by standard deviation of lateral position (SDLP) are shown. In the right panel, the single and combined effects of MDMA and alcohol on SDLP are shown. D1 = Day 1, D2 = Day 2; NA = No alcohol, A = Alcohol; MPH = methylphenidate.

with alcohol, MDMA counteracted the effects of the alcohol-induced sedation and lack of energy. In addition, and similar to the results of Hernandez and colleagues [37], Kuypers and colleagues [27] showed that MDMA counteracted the subjective effects of alcohol, while the psychomotor performance was still impaired.

Methodological issues in MDMA research

An important question that has to be asked is what the relevance of all these results mentioned above is for drug driving in real life. An important remark that has to be made, addressing all these studies, is that the drug effects assessed in these studies will always be an underrepresentation of the effects found in the real world. The reason for this is that performance was tested under (semi-) controlled circumstances. This implicates that the results found in these studies are only true for these particular situations and doses. There are numerous factors related to the drug, the individual and the situation that can influence the effects of ecstasy, and drugs in general, on driving performance in the "real world"[42]. Drug-related examples are the purity of the drug, the dose and the interaction with other substances. Examples related to the individual are tolerance and sensitivity for the drug. Examples of situation-related factors are the number of hours between consumption of the drug and driving, state of mind, distraction from the driving task due to passengers. These issues will be discussed in depth in the following paragraphs.

MDMA dose and consumption pattern

In the introduction it was already pointed out that administration of multiple ecstasy pills at once (stacking) or at several successive time points during the night (boosting) is common practice among ecstasy users [11]. Survey study data have shown that the median number of pills taken per occasion is two [9, 43] and that heavy users tend to take more pills on each occasion [9]. The consumption pattern seems to change with repeated use, i.e. a commonly reported phenomenon is an increase in amounts of tablets taken since first use [44, 45]. A possible reason for this is the indication that positive effects of MDMA subside with repeated use [44]. Users state that they become tolerant to the subjective effects and have to increase their dose to feel the same way as they did the first time [45]. This reduction of positive effects goes together with a boost in negative side effects. An important question inextricably bound up with the tolerance for positive effects is whether it is accompanied by a tolerance for performance impairment. This question of behavioral tolerance has never been addressed in experimental studies. Evidently this is an important topic as an absence of behavioral tolerance in subjects with tolerance for subjective effects will lead to a substantial greater impairment perhaps not noticed by the users themselves. Interwoven with this is the phenomenon that ecstasy users self-administrate single high doses of MDMA. Apart from one study investigating the

pharmacokinetic effects of ecstasy with a dose range of 50–150 mg [46] none of the studies presented in this chapter addressed the performance effects after single high dosing per session. All of the studies administered a single and relatively low dose. The study with the highest dose (i.e. MDMA-150) showed that this dose produced several cardiovascular and subjective side effects [46]. In real life, this dose is the equivalent of two ecstasy pills as it was previously shown that the average MDMA concentration in an ecstasy tablet is 75 mg [47].

Performance after boosting (repeated MDMA dosing) has previously been studied under controlled experimental circumstances [28, 48]. However as with the single dose studies, the doses were kept low, i.e. 75 and 50 mg to circumvent possible negative side effects as previously described by de la Torre and colleagues [46]. Nevertheless, as the percentage of heavy users is increasing [9, 43] this implicates that the behavioral effects mentioned in the studies are not true for this sample. Unfortunately it will not be possible due to medical and ethical constraints to investigate high dose effects under controlled conditions. However, the studies mentioned above did reveal on what kind of behavior MDMA exerts its effects and case studies have shown that risk behavior increases after high doses of MDMA. This is evidence enough to prove that the effects of high doses of MDMA are a hazard for traffic safety.

Co-use of multiple drugs

A second issue mentioned in the introduction was the fact that co-use of other substances with ecstasy is common practice [9]. Ecstasy tends to be combined with both "uppers"/stimulant drugs such as amphetamine and cocaine as with "downers" or hallucinogens such as alcohol, cannabis and LSD. Partygoers indicated on a questionnaire that the co-use occurs while ecstasy is still having its effects [43]. It is evident that these additional substances also exert particular effects on performance and that the performance outcome after a combination could be totally different compared with the effects of ecstasy alone. These combination effects could be additional or synergistic to the single ecstasy effects. The one combination that has been investigated to date is that of alcohol with MDMA [27, 33, 37]. An important fact is that pharmacokinetic profiles of combined substances could be influenced by co-administration of substances. Hernandez-Lopez and colleagues showed an increase of plasma concentrations of MDMA by 13% when combining a 100 mg dose of MDMA with 0.8 g/kg ethanol [37]. Kuypers and colleagues also found increases of 7% and 8.7% when MDMA (75 mg and 100 mg) was combined with alcohol [27]. However, in contrast with Hernandez and colleagues, these increases were not statistically significant. The difference between the two studies is that the blood alcohol levels were not equally high, i.e. 0.115 g/dl [27] *vs*. approximately 0.04 g/dl [37] and this could perhaps explain the difference in results.

It is evident that another kind of impairment (perhaps more extreme) has to be anticipated after combined use of several substances. It is clear that future studies have to address this issue and that the spectrum of combinations certainly needs to be broadened.

Controlled environment during driving tests

Characteristic of all experimental studies is that testing occurs under controlled circumstances and subjects are submitted to certain rules. This has the advantage that subjective and objective performance effects are in total attributable to the study drug and not some confounding factors. The drawback of this is that generalization of the data to real world situations is not always evident. In the following, the driving task is taken as an example to illustrate this point.

During the driving task subjects are not allowed to talk and they have to keep the speed of the car at a constant predefined value, i.e. 95 km/h. The advantage of the ban on speaking is that the subject is not distracted from the main task and their attention can be fully directed at the driving task. In real life, however, multiple distractions will be present during driving such as talking passengers in the car, eating, drinking, mobile phone, a radio switched on, etc. Second, it was mentioned that subjects have to keep constant speed. Every attempt at speeding will hereby nipped in the bud by this rule, or otherwise by the driving instructor. Previously however speeding and display of risky behavior was observed in people driving under the influence of ecstasy and ecstasy users reported a tendency to speed and a slowing of reaction speed after they had used ecstasy [17, 18, 42]. The speeding and the risky behavior are two types of dangerous behavior that can increase the risk of having a car accident. This type of behavior cannot be tested on the road as it poses too many risks on safety. Both types of behavior can be implemented in the laboratory by means of computer tasks or simulated driving. The disadvantage associated with the driving simulator is that the possibilities with the simulated driving scenario are limited and it has to be assured that the scenario does not become too predictable but is comparable over several test conditions and subjects. The disadvantage of both types of tasks is that the "real-life feeling" cannot be induced; it always stays an artificial setting and subjects will never behave the same way as they would in real life.

Time of day of drug driving/subjective judgment

In all of the experimental studies discussed above, performance effects of MDMA were mainly studied during peak blood concentrations or in a window close to peak concentrations. Since most ecstasy users either take the tablets at home just before going to the party or they take the tablets at the party and drive home afterwards, hours after intake, it is doubtful that they will drive when the MDMA concentrations in blood are maximal or close to maximum [4].

A survey study among partygoers revealed that some of the interviewees based their decision of whether they would drive on their subjective feeling of impairment, i.e. they only drove when they knew the effects had worn off. Others based their decision on the pharmacokinetics of the drug, i.e. they discriminated three phases. The first phase was 30 minutes after intake when the estimated chance of impairment was relatively low as there were yet no drug effects. The second phase was between 30 minutes and 2 h post-drug; they judged that in this interval the

chance of being impaired was the highest as the effects were rising. The third phase was after three hours; they believed that most of the effects were gone at that moment because they were in the "coming-down" phase. [42]. The subjects in the previously described driving studies [26, 27, 35] drove between three and five hours post-drug, i.e. in the interval that a number of interviewed ecstasy users in the study of Neale [42] addressed as the safest period to drive. The results of the driving studies indicated that there were still measurable drug effects on driving performance in that particular time frame. Performance under automated control did not suffer as much under influence of MDMA whereas heavier demand skills were somewhat impaired. In spite of the fact that partygoers in the study of Neale depicted the period after 3 hours post-drug as relatively safe, reportage of negative experiences with driving under influence of ecstasy was not uncommon. The perceived effects ranged from impairment of mental functions (e.g. fear, hallucinations) and visual functions (e.g. blurred vision) to impairment of motor performance, e.g. tendency to speed and slower reaction times [42].

Driving after prolonged dancing and lack of sleep

The main motives for ecstasy use at parties are to experience the energetic and euphoric effects of MDMA. The users take the drug to be able to dance all night long and to feel good [1]. A survey study on a party in the Netherlands showed that a substantial amount of interviewed partygoers (72 %) reported they danced at least half the evening [9]. There are thus at least two factors that can have an additional impact on performance after partying a night on ecstasy. First of all, as people stay all night they will be sleep deprived. Interviewed partygoers who indicated that they drove after taking ecstasy did so between 2 a.m. and 12 a.m. on Saturdays and Sundays [42]. A study comparing the single effects of alcohol intoxication and sleep deprivation on performance showed that moderate levels of fatigue produced higher levels of impairment than the legally permitted level of alcohol intoxication. Performance on a tracking task decreased with 0.74 % per hour between the 10^{th} (6 p.m.) and 26^{th} (10 a.m.) hour of wakefulness. After 17 hours of wakefulness (3 a.m.) performance was comparable to performance under influence of 0.05 % blood alcohol [49]. Previous experimental studies (except one) were conducted during daytime, when subjects had a night of good sleep; it is evident that further research on the effects of sleep deprivation after MDMA intake on driving-related performance and actual driving performance is wanted. Besides sleep deprivation, which evidently has an impact on performance, the prolonged exertion (dancing) will act as an energy drain. This might have additional effects on performance next to the sleep deprivation. Research in this area is lacking but wanted as it will provide a better approximation of the real-life situation.

Conclusion

The studies mentioned above have shown that ecstasy affects driving-related performance and driving performance in several ways. Results from the driving tests showed that the stimulating effects of two particular doses of MDMA were found only on the lowest or operational level of the driving task under optimal driving conditions, i.e. daytime, lower than average speed compared to other traffic, low level of interaction with traffic. In real life, conditions are not that optimal as people tend to combine several substances, perhaps take additional doses of ecstasy and drive at nighttime at higher speeds than the set limit during the driving test. These are all factors that could affect different levels of the driving task in a negative way. It was shown that certain measures of cognitive and psychomotor performance improved after MDMA administration as indicated by increased impulse control and improved tracking. This was only when conditions were optimal, i.e. daytime performance and low doses of MDMA. Several performance measures after a dose of MDMA in combination with an arousal/activation-lowering manipulation, i.e. a low dose of alcohol or sleep deprivation, were impaired. Measures of subjective impairment however demonstrated that subjects did not notice this impairment. This discrepancy between objective and subjective measures is an issue that deserves extra attention as subjects are apparently not able to self-judge the extent of their objective impairment. In real life, subjects tend to rely on subjective feelings to decide whether they find themselves able to drive a car. This can be very dangerous, certainly when subjects have mixed several drugs, are sleep deprived, and want to drive home after a party, which is the situation every weekend. Future studies combining MDMA with THC or amphetamines could provide very useful information because these substances have mainly different pharmacodynamic properties, and therefore the effects on psychomotor and cognitive measures could be widespread. This could have serious implications in real life, when people try to conduct a vehicle under the influence of this party cocktail of drugs. When studying the effects of these combinations it would also be interesting to add some factors related to the "party lifestyle" of ecstasy users, i.e. sleep deprivation, and prolonged physical exertion, to increase the ecological validity of the experimental studies. Consequently this will provide more insight in the real-life situation.

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Appendix I
ICADTS Drug List 2007

Disclaimer: Although the information presented below has been gathered and evaluated with great care, ICADTS will not accept any liability after use of the information by patients taking the medicines listed.

Note: The application of the ICADTS list without reading this background information will limit the use of the various advices provided to physicians and pharmacists. Therefore it is strongly recommended to read the full document before using the ICADTS list.

Introduction

After the publication of the report of the ICADTS Working Group on Prescribing and Dispensing Guidelines for Medicinal Drugs affecting Driving Performance in 2001 (see www.icadts.org), it was discussed that a list with medicinal drugs categorized according to their impairing properties was needed. The practical use of the guidelines would benefit from the availability of such a list, because it would allow the prescribing doctor and dispensing pharmacist to look for safer alternatives within one specific therapeutic class.

Descriptions of categories

Ever since the development of a list according to the impairing properties of medicinal drugs in 1991 (Wolschrijn et al.), three European countries introduced their list based on the original proposal by Wolschrijn et al. Belgium was the first to publish an updated list in 1999, Spain followed in 2002, and France recently in 2005 introduced a more extensive list.

Belgium and Spain applied the original descriptions of the categorizations in their publications, whereas France used a different approach. The original descriptions of impairment of driving performance or performance related to driving as described by Wolschrijn et al. have been summarized in the European Note for Guidance for the Summary of Product Characteristics (III/9163/90-EN, Final approval 16th October 1991) for use in the package inserts of medicinal drugs into:

1. Presumed to be safe or unlikely to produce an effect;
2. Likely to produce minor or moderate adverse effects;
3. Likely to produce severe effects or presumed to be potentially dangerous.

Ever since many articles have been published where the practical implications of this three-tier categorization system were illustrated by comparing the effects within the three categories with the effect of different blood alcohol concentrations (BAC). Based on experimental work in the Netherlands with over-the-road driving tests the calibration was introduced for categories I, II and III as respectively equivalent to BACs < 0.5 g/l (<0.05%), 0.5–0.8 g/l (0.05–0.08%), > 0.8 g/l (>0.08%).

It was decided by the experts from the ICADTS working group to use this calibration scheme as part of the clarification of the terminology of the three categories, because this was considered to be more meaningful since 0.5 g/l is the legal limit in the vast majority of EU countries. Although the Belgian categorizations were described as the original and extensive ones as suggested by Wolschrijn et al. in 1991, and used for the purpose to achieve consensus among international experts, it is easier to read the categories by using a more condensed description. This is the case with the Spanish descriptions that are the summarized ones as being used by the EU's Committee for Proprietary Medicinal Products in its Note for Guidance (see above).

The French descriptions are somewhat different because they are considering the perspective of the patient allowing him or her to act and to decide on the best way to respond to the warning given for a specific category. But basically the idea behind it is not so different, it is more focussing on the practical use of the various categories, which is an advantage. It also takes into account the judgement of the physician.

Although these differences in descriptions exist, it is possible to agree on the categorizations based on existing systems in the various countries, and therefore the ICADTS Working Group has proposed the following descriptions for using its list:

Description of category	Interpretation and practical use
Category I: Presumed to be safe or unlikely to produce an effect	In various experimental circumstances negligible or no impairment of driving performance or performance related to driving is repeatedly demonstrated. Also for medicinal drugs that are presumed not to be dangerous based on their pharmacological profile, even though there are no experimental studies that support this presumption. For the most frequently used drugs in this category the effect has been assessed in over-the-road driving tests as equivalent to blood alcohol concentrations < 0.5 g/l (<0.05%). *Advice for the patient:* Be careful not to drive before having read the warnings in the package insert.
Category II: Likely to produce minor or moderate adverse effects	Some impairment of driving performance or performance related to driving is seen in various experimental laboratory circumstances. Also for drugs that will not produce severely adverse effects, but because of a lack of sufficient experimental studies it can not be established if the effect is moderate, light or absent. For the most frequently used drugs in this category the effect has been assessed in over-the-road driving tests as equivalent to blood alcohol concentrations 0.5–0.8 g/l (0.05–0.08%). *Advice for the patient:* Do not drive without consulting a healthcare professional about the possible impairing effects.
Category III: Likely to produce severe effects or presumed to be potentially dangerous	In various experimental circumstances gross impairment of driving performance, or performance related to driving, is repeatedly seen. Also for drugs presumed to be potentially dangerous based upon their pharmacological profile, but there are not sufficient experimental studies to support this presumption. For the most frequently used drugs in this category the effect has been assessed in over-the-road driving tests as equivalent to blood alcohol concentrations > 0.8 g/l (>0.08%). *Advice for the patient:* Do not drive when this drug is taken and consult a healthcare professional when to start driving again after evaluation of the treatment outcomes.

Limitations of the ICADTS list

It is not the objective of the ICADTS Working Group to review all available literature again in assigning categories for medicinal drugs and thereby duplicating the work that has been done in Belgium, Spain and France, respectively in 1999, 2002 and 2005.
An updated review will be done in the near future within the Sixth Framework Programme of the European Union as an Integrated Project entitled DRUID (Driving under the Influence of Drugs, Alcohol and Medicines) that has started in September 2006.

Furthermore, the list will only contain medicinal drugs which are on the market in either, Belgium, Spain or France and therefore will not cover all drugs within a therapeutic class.

Another limitation is the lack of information in the categories on the various dosages that are used for the different medicinal drugs. *As a general rule the categories are assigned to the drug in the normal therapeutic dosage given to an adult person for the main indication of the drug*. If higher dosages are taken one should consider the drug to be categorized as being one category higher if not yet assigned to the highest category.

Wolschrijn H, De Gier JJ and De Smet PAGM. Drugs and driving: a new categorization system for drugs affecting psychomotor performance. Institute for Drugs, Safety and Behavior, University of Limburg, The Netherlands, 1991. Tech Report.

ATC	Substance Name		Category
A Alimentary Tract And Metabolism			
A02 Drugs For Acid Related Disorders			
A02B	***Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)***		
A02BA	*H2-receptor antagonists*		
	A02BA01	Cimetidine	I
	A02BA02	Ranitidine	I
	A02BA03	Famotidine	II
	A02BA04	Nizatidine	II
	A02BA06	Roxatidine	I
A03 Drugs For Functional Gastrointestinal Disorders			
A03F	Propulsives		
A03FA	*Propulsives*		
	A03FA01	Metoclopramide	II

ATC	Substance Name		Category
A04 Antiemetics And Antinauseants			
A04A	***Antiemetics and antinauseants***		
A04AA	*Serotonin (5HT3) antagonists*		
	A04AA01	Ondansetron	I
	A04AA02	Granisetron	I
	A04AA03	Tropisetron	I
	A04AA04	Dolasetron	I
A04AD	*Other antiemetics*		
	A04AD01	Scopolamine	II
	A04AD05	Metopimazine	II
		Dimenhydrinate (= diphenhydramine theoclate)	III
A08 Antiobesity Preparations, Excl Diet Products			
A08A	***Antiobesity preparations, excl dietary products***		
A08AA	*Centrally acting antiobesity products*		
	A08AA01	Phentermine	I
	A08AA03	Amfepramone	I
	A08AA06	Etilamfetamine	I
	A08AA08	Clobenzorex	I
A10 Drugs Used In Diabetes			
A10A	***Insulins and analogues***		category II for this class of drugs is meant to advise patients to consult their physician before driving about possible impairing conditions while using the drug
		Insulin	II
A10AB	*Insulins and analogues, fast-acting*		
	A10AB01	Insulin (human)	II
	A10AB04	Insulin lispro	II
	A10AB05	Insuline aspart	II
A10AC	*Insulins and analogues, intermediate-acting*		
	A10AC01	Insuline (human)	II
	A10AC04	Insuline lispro	II
A10AD	*Insulins and analogues, intermediate-acting combined with fast-acting*		
	A10AD01	Insuline (human)	II
	A10AD04	Insuline lispro	II
	A10AD30	Combinations	II

ATC	Substance Name		Category
A10AE	*Insulins and analogues, long-acting*		
	A10AE01	Insuline (human)	II
	A10AE04	Insuline glargine	II
	A10AE05	Insuline detemir	II
A10B	***Oral blood glucose lowering drugs***		category II for this class of drugs is meant to advise patients to consult their physician before driving about possible impairing conditions while using the drug
A10BA	*Biguanides*		
	A10BA01	Phenformin	II
	A10BA02	Metformin	II
	A10BA03	Buformin	II
A10BB	*Sulfonamides, urea derivatives*		
	A10BB01	Glibenclamide	II
	A10BB02	Chlorpropamide	II
	A10BB03	Tolbutamide	II
	A10BB04	Glibornuride	II
	A10BB06	Carbutamide	II
	A10BB07	Glipizide	II
	A10BB08	Gliquidone	II
	A10BB09	Gliclazide	II
	A10BB12	Glimepiride	II
		Glisentide	II
A10BD	*Combinations of oral blood glucose lowering drugs*		
	A10BD01	Phenformin and sulfonamides	II
	A10BD02	Metformin and sulfonamides	II
	A10BD03	Metformin and rosiglitazone	II
A10BF	*Alpha glucosidase inhibitors*		
	A10BF01	Acarbose	II
A10BX	*Other oral blood glucose lowering drugs*		
	A10BX02	Repaglinide	II
	A10BX03	Nateglinide	II

ATC	Substance Name		Category
C Cardiovascular System			
C07 Beta Blocking Agents			
C07A	***Beta blocking agents***		
C07AA	*Beta blocking agents, non-selective*		
	C07AA01	Alprenolol	I
	C07AA02	Oxprenolol	II
	C07AA03	Pindolol	II
	C07AA05	Propranolol	II
	C07AA06	Timolol	II
	C07AA07	Sotalol	I
	C07AA12	Nadolol	II
	C07AA16	Tertatolol	II
C07AB	*Beta blocking agents, selective*		
	C07AB02	Metoprolol	II
	C07AB03	Atenolol	I
	C07AB04	Acebutolol	I
	C07AB05	Betaxolol	I
	C07AB07	Bisoprolol	I
	C07AB08	Celiprolol	I
	C07AB12	Nebivolol	II
C07AG	*Alpha and beta blocking agents*		
	C07AG01	Labetalol	I
	C07AG02	Carvedilol	II
G Genito Urinay System And Sex Hormones			
G02 Other Gynecologicals			
G02C	***Other gynecologicals***		
G02CB	*Prolactine inhibitors*		
	G02CB02	Lisuride	II
H Systemic Hormonal Preparations, Excl Sex Hormones And Insulins			
H04 Pancreatic Hormones			
H04A	***Glycogenolytic hormones***		category II for this class of drugs is meant to advise patients to consult their physician before driving about possible impairing conditions while using the drug
H04AA	*Glycogenolytic hormones*		
	H04AA01	Glucagon	II

ATC	Substance Name		Category
M Musculo-Skeletal System			
M01 Antiinflammatory And Antirheumatic Products			
M01A	***Antiinflammatory and antirheumatic products, non-steroids***		
M01AB	*Acetic acid derivatives and related substances*		
	M01AB05	Diclofenac	I
M01AE	*Propionic acid derivatives*		
	M01AE01	Ibuprofen	I
	M01AE02	Naproxen	I
	M01AE03	Ketoprofen	I
	M01AE04	Fenoprofen	I
M01AG	*Fenamates*		
	M01AG01	Mefenamic acid	I
M01AH	*Coxibs*		
	M01AH04	Parecoxib	I
M03 Muscle Relaxants			
M03B	***Muscle relaxants, centrally acting agents***		
M03BX	*Other centrally acting agents*		
	M03BX07	Tetrazepam	II
N Nervous System			
		Phendimetrazine	I
N01 Anesthetics			
N01A	***Anesthetics, general***		
N01AB	*Halogenated hydrocarbons*		
	N01AB01	Halothane	III
	N01AB04	Enflurane	III
	N01AB06	Isoflurane	III
	N01AB07	Desflurane	III
	N01AB08	Sevoflurane	III
N01AF	*Barbiturates, plain*		
	N01AF03	Thiopental	III
N01AH	*Opioid anesthetics*		
	N01AH01	Fentanyl	III
	N01AH02	Alfentanil	III
	N01AH03	Sufentanil	III
	N01AH06	Remifentanil	III

ATC	Substance Name		Category	
N01AX	*Other general anesthetics*			
	N01AX03	Ketamine	III	
	N01AX07	Etomidate	III	
	N01AX10	Propofol	III	
	N01AX13	Nitrous oxide	II	
N01B	***Anesthetics, local***			
N01BA	*Esters of aminobenzoic acid*			
	N01BA02	Procaine	II	
N01BB	*Amides*			
	N01BB01	Bupivacaine	III	
	N01BB02	Lidocaine	II	
	N01BB03	Mepivacaine	II	
	N01BB08	Articaine	II	
	N01BB09	Ropivacaine	II	
	N01BB51	Bupivacaine, combinations	II	
	N01BB52	Lidocaine, combinations	II	
	N01BB53	Mepivacaine, combinations	II	
	N01BB58	Articaine, combinations	II	
N02 Analgesics				
N02A	***Opioids***			
N02AA	*Natural opium alkaloids*			
	N02AA01	Morphine	III	
	N02AA03	Hydromorphone	II	
	N02AA05	Oxycodone	II	
	N02AA08	Dihydrocodeine	II	
	N02AA59	Codeine, combinations excl psycholeptics	II	Category I for < 20 mg codeine base
N02AB	*Phenylpiperidine derivatives*			
	N02AB02	Pethidine	III	
	N02AB03	Fentanyl	III	
N02AC	*Diphenylpropylamine derivatives*			
	N02AC01	Dextromoramide	III	
	N02AC03	Piritramide	III	
	N02AC04	Dextropropoxyphene	II	
	N02AC05	Bezitramide	III	
	N02AC54	Dextropropoxyphene comb. excl psycholeptics	II	
N02AD	*Benzomorphan derivatives*			
	N02AD01	Pentazocine	III	

ATC	Substance Name		Category	
N02AE	*Oripavine derivatives*			
	N02AE01	Buprenorphine	III	for analgetic use
N02AF	*Morphinan derivatives*			
	N02AF02	Nalbuphine	II	
N02AX	*Other opioids*			
	N02AX01	Tilidine	III	
	N02AX02	Tramadol	III	
	N02AX52	Tramadol, combinations	III	
N02B	***Other analgesics and antipyretics***			
N02BA	*Salicylic acid and derivatives*			
	N02BA51	Acetylsalicylic acid, combinations excl psycholeptics	II	Category I for < 20 mg codeine base
N02BE	*Anilides*			
	N02BE51	Paracetamol, combinations excl psycholeptics	II	Category I for < 20 mg codeine base
N02BG	*Other analgesics and antipyretics*			
	N02BG04	Floctafenine	I	
N02C	***Antimigraine preparations***			
N02CA	*Ergot alkaloids*			
	N02CA52	Ergotamine, combinations excl psycholeptics	I	
N02CC	*Selective serotonin (5HT1) agonists*			
	N02CC01	Sumatriptan	II	
	N02CC02	Naratriptan	II	
	N02CC03	Zolmitriptan	II	
	N02CC04	Rizatriptan	II	
	N02CC05	Almotriptan	II	
	N02CC06	Eletriptan	II	
	N02CC07	Frovatriptan	II	
N02CX	*Other antimigraine preparations*			
	N02CX01	Pizotifen	II	
	N02CX06	Oxetorone	II	

ATC	Substance Name		Category
N03 Antiepileptics			
N03A	***Antiepileptics***		
N03AA	*Barbiturates and derivatives*		
	N03AA01	Methylphenobarbital	II
	N03AA02	Phenobarbital	III
	N03AA03	Primidone	III
N03AB	*Hydantoin derivatives*		
	N03AB02	Phenytoin	III
	N03AB05	Fosphenytoin	III
N03AD	*Succinimide derivatives*		
	N03AD01	Ethosuximide	II
N03AE	*Benzodiazepine derivatives*		
	N03AE01	Clonazepam	II
N03AF	*Carboxamide derivatives*		
	N03AF01	Carbamazepine	II
	N03AF02	Oxcarbazepine	II
N03AG	*Fatty acid derivatives*		
	N03AG01	Valproic acid	II
	N03AG02	Valpromide	II
	N03AG04	Vigabatrin	II
	N03AG05	Progabide	II
	N03AG06	Tiagabine	II
N03AX	*Other antiepileptics*		
	N03AX09	Lamotrigine	II
	N03AX10	Felbamate	II
	N03AX11	Topiramate	II
	N03AX12	Gabapentin	II
	N03AX13	Pheneturide	II
	N03AX14	Levetiracetam	II
N04 Anti-Parkinson Drugs			
N04A	***Anticholinergic agents***		
N04AA	*Tertiary amines*		
	N04AA01	Trihexyphenidyl	II
	N04AA02	Biperiden	II
	N04AA12	Tropatepine	II

ATC	Substance Name		Category
N04B	***Dopaminergic agents***		
N04BA	*Dopa and dopa derivatives*		
	N04BA02	Levodopa and decarboxylase inhibitor	II
	N04BA03	Levodopa, decarboxylase inhibitor and COMT inhibitor	II
N04BB	*Amantadene derivatives*		
	N04BB01	Amantadine	I
N04BC	*Dopamine agonists*		
	N04BC01	Bromocriptine	II
	N04BC02	Pergolide	II
	N04BC04	Ropinirole	II
	N04BC05	Pramipexole	II
	N04BC06	Cabergoline	II
	N04BC07	Apomorphine	II
N04BD	*Monoamine oxidase B inhibitors*		
	N04BD01	Selegiline	I
N04BX	*Other dopaminergic agents*		
	N04BX02	Entacapone	II
N05 Psycholeptics			
N05A	***Antipsychotics***		
N05AA	*Phenothiazines with aliphatic side-chain*		
	N05AA01	Chlorpromazine	III
	N05AA02	Levomepromazine	III
	N05AA03	Promazine	III
	N05AA06	Cyamemazine	III
N05AB	*Phenothiazines with piperazine structure*		
	N05AB01	Dixyrazine	II
	N05AB02	Fluphenazine	II
	N05AB03	Perphenazine	II
	N05AB06	Trifluoperazine	III
	N05AB08	Thioproperazine	III
N05AC	*Phenothiazines with piperidine structure*		
	N05AC01	Periciazine	III
	N05AC02	Thioridazine	III
	N05AC04	Pipotiazine	III

ATC	Substance Name		Category
N05AD	*Butyrophenone derivatives*		
	N05AD01	Haloperidol	II
	N05AD02	Trifluperidol	II
	N05AD03	Melperone	II
	N05AD05	Pipamperone	II
	N05AD06	Bromperidol	II
	N05AD07	Benperidol	II
	N05AD08	Droperidol	II
	N05AD09	Fluanisone	III
N05AE	*Indole derivatives*		
	N05AE03	Sertindole	II
N05AF	*Thioxanthene derivatives*		
	N05AF01	Flupentixol	II
	N05AF05	Zuclopentixol	II
N05AG	*Diphenylbutylpiperidine derivatives*		
	N05AG01	Fluspirilene	II
	N05AG02	Pimozide	II
	N05AG03	Penfluridol	II
N05AH	*Diazepines, oxazepines and thiazepines*		
	N05AH01	Loxapine	III
	N05AH02	Clozapine	II
	N05AH03	Olanzapine	II
	N05AH04	Quetiapine	II
N05AL	*Benzamides*		
	N05AL01	Sulpiride	II
	N05AL02	Sultopride	II
	N05AL03	Tiapride	II
	N05AL05	Amisulpride	II
	N05AL06	Veralipride	II
N05AN	*Lithium*		
	N05AN01	Lithium	II
N05AX	*Other antipsychotics*		
	N05AX07	Prothipendyl	III
	N05AX08	Risperidone	II
	N05AX09	Clotiapine	II

ATC	Substance Name		Category
N05B	***Anxiolytics***		
N05BA	*Benzodiazepine derivatives*		
	N05BA01	Diazepam	III
	N05BA02	Chlordiazepoxide	III
	N05BA03	Medazepam	II
	N05BA04	Oxazepam	III
	N05BA05	Potassium clorazepate	II
	N05BA06	Lorazepam	III
	N05BA08	Bromazepam	III
	N05BA09	Clobazam	II
	N05BA10	Ketazolam	III
	N05BA11	Prazepam	II
	N05BA12	Alprazolam	III
	N05BA13	Halazepam	III
	N05BA14	Pinazepam	III
	N05BA15	Camazepam	II
	N05BA16	Nordazepam	II
	N05BA18	Ethyl loflazepate	II
	N05BA21	Clotiazepam	III
	N05BA22	Cloxazolam	II
	N05BA23	Tofisopam	II
		Bentazepam	III
N05BB	*Diphemylmethane derivatives*		
	N05BB01	Hydroxyzine	III
	N05BB02	Captodiame	I
N05BC	*Carbamates*		
	N05BC01	Meprobamate	III
N05BE	*Azaspirodecandione derivatives*		
	N05BE01	Buspirone	I
N05BX	*Other anxiolytics*		
	N05BX03	Etifoxine	I
N05C	***Hypnotics and sedatives***		
N05CA	*Barbiturates, plain*		III
	N05CA02	Amobarbital	III
	N05CA03	Butobarbital	III
	N05CA06	Secobarbital	III
		Brallobarbital	III

ATC	Substance Name		Category	
N05CD	*Benzodiazepine derivatives*			
	N05CD01	Flurazepam	III	
	N05CD02	Nitrazepam	III	
	N05CD03	Flunitrazepam	III	
	N05CD04	Estazolam	III	
	N05CD05	Triazolam	III	
	N05CD06	Lormetazepam	III	1 mg (capsule): >10 hours post dosing little or no impairment (Category I)
	N05CD07	Temazepam	III	10 mg: >10 hours post dosing little or no impairment (Category I)
	N05CD08	Midazolam	III	
	N05CD09	Brotizolam	III	
	N05CD10	Quazepam	III	
	N05CD11	Loprazolam	III	
N05CF	*Benzodiazepine related drugs*			
	N05CF01	Zopiclon	III	
	N05CF02	Zolpidem	II	10 mg: >10 hours post dosing little or no impairment (Category I)
	N05CF03	Zaleplon	II	10 mg: >5 hours post dosing little or no impairment (Category I)
N05CM	*Other hypnotics and sedatives*			
	N05CM16	Niaprazine	III	
N05CX	*Hypnotics and sedatives in combination, excl barbiturates*			
	N05CX01	Meprobamate, combinations	III	

ATC	Substance Name		Category
N06 Psychoanaleptics			
N06A	***Antidepressants***		
N06AA	*Non-selective monoamine reuptake inhibitors*		
	N06AA01	Desipramine	II
	N06AA02	Imipramine	II
	N06AA04	Clomipramine	II
	N06AA05	Opipramol	II
	N06AA06	Trimipramine	III
	N06AA07	Lofepramine	II
	N06AA09	Amitriptyline	III
	N06AA10	Nortriptyline	II
	N06AA12	Doxepin	III
	N06AA14	Melitracen	II
	N06AA16	Dosulepin	III
	N06AA17	Amoxapine	III
	N06AA19	Amineptine	II
	N06AA21	Maprotiline	II
N06AB	*Selective serotonin reuptake inhibitors*		
	N06AB03	Fluoxetine	I
	N06AB04	Citalopram	I
	N06AB05	Paroxetine	I
	N06AB06	Sertraline	I
	N06AB08	Fluvoxamine	I
	N06AB10	Escitalopram	I
N06AF	*Monoamine oxidase inhibitors, non-selective*		
	N06AF02	Nialamide	II
	N06AF03	Phenelzine	II
	N06AF04	Tranylcypromine	II
	N06AF05	Iproniazide	II
	N06AF06	Iproclozide	II
N06AG	*Monoamine oxidase A inhibitors*		
	N06AG02	Moclobemide	I
	N06AG03	Toloxatone	II
N06AX	*Other antidepressants*		
	N06AX03	Mianserin	III
	N06AX05	Trazodone	III
	N06AX06	Nefazodone	II
	N06AX09	Viloxazine	II
	N06AX11	Mirtazapine	III
	N06AX14	Tianeptine	II
	N06AX16	Venlafaxine	I
	N06AX17	Milnacipran	II
	N06AX18	Reboxetine	I

ATC	Substance Name		Category	
N06B	***Psychostimulants, agents used for ADHD and nootropics***			
N06BA	*Centrally acting sympathicomimetics*			
	N06BA01	Amfetamine	II	
	N06BA02	Dexamfetamine	II	
	N06BA04	Methylphenidate	I	
	N06BA05	Pemoline	I	
	N06BA10	Fenetylline	I	
		Fenproporex	I	
N06BX	*Other psychostimulants and nootropics*			
	N06BX03	Piracetam	II	
	N06BX14	Prolintane	I	
N06D	***Anti-dementia drugs***			
N06DA	*Anticholinesterases*			
	N06DA02	Donezepil	II	
	N06DA03	Rivastigmine	II	
	N06DA04	Galantamine	II	
N06DX	*Other anti-dementia drugs*			
	N06DX01	Memantine	II	
N07 Other Nervous System Drugs				
N07B	***Drugs used in addictive disorders***			
N07BA	*Drugs used in nicotine dependence*			
	N07BA02	Bupropion	II	
N07BB	*Drugs used in alcohol dependence*			
	N07BB01	Disulfiram	II	
	N07BB04	Naltrexone	II	
N07BC	*Drugs used in opioid dependence*			
	N07BC01	Buprenorphine	II	for use in opioid dependence
	N07BC02	Methadone	II	
N07C	***Antivertigo preparations***			
N07CA	*Antivertigo preparations*			
	N07CA01	Betahistine	I	
	N07CA02	Cinnarizine	II	
	N07CA03	Flunarizine	II	
N07X	***Other nervous system drugs***			
N07XX	*Other nervous system drugs*			
	N07XX02	Riluzole	I	

ATC	Substance Name		Category	
R Respiratory System				
R01 Nasal Preparations				
R01A	***Decongestants and other nasal preparations for topical use***			
R01AC	*Antiallergic agents, excl corticosteroids*			
	R01AC02	Levocabastine	I	
R01BA	***Nasal decongestants for systemic use***			
R01BA	*Sympathicomimetics*			
	R01BA01	Phenylpropanolamine	I	
R05 Cough And Cold Preparations				
R05D	***Cough suppressants, excl combinations with expectorants***			
R05DA	*Opium alkaloids and derivatives*			
	R05DA01	Ethylmorphine	III	
	R05DA03	Hydrocodon	II	
	R05DA04	Codeine	II	Category I for < 20 mg codeine base
	R05DA07	Noscapine	I	
	R05DA08	Pholcodine	II	
	R05DA09	Dextrometorphan	I	
	R05DA10	Thebacon	II	
	R05DA12	Acetyldihydrocodeine	II	
R05DB	*Other cough suppressants*			
	R05DB03	Clobutinol	I	
	R05DB05	Pentoxyverine	I	
R05F	***Cough suppressants and expectorants, combinations***			
R05FA	*Opium derivatives and expectorants*			
	R05FA02	Opium derivatives and expectorants	II	
R05FB	*Other cough suppressants and expectorants*			
	R05FB01	Cough suppressants and mucolytics	II	
	R05FB02	Cough suppressants and expectorants	II	

ATC	Substance Name		Category
R06 Antihistamines For Systemic Use			
R06A	***Antihistamines for systemic use***		
R06AA	*Aminoalkyl ethers*		
	R06AA02	Diphenhydramine	III
	R06AA04	Clemastine	III
	R06AA06	Chlorphenoxamine	II
	R06AA08	Carbinoxamine	II
	R06AA09	Doxylamine	III
R06AB	*Substituted alkylamines*		
	R06AB01	Brompheniramine	II
	R06AB02	Dexchlorpheniramine	II
	R06AB04	Chlorphenamine	II
	R06AB05	Pheniramine	II
	R06AB52	Dexchlorpheniramine, combinations	II
	R06AB54	Chlorphenamine, combinations	II
R06AC	*Substituted ethylene diamines*		
	R06AC02	Histapyrrodine	II
R06AD	*Phenothiazine derivatives*		
	R06AD01	Alimemazine	III
	R06AD02	Promethazine	III
	R06AD07	Mequitazine	II
	R06AD09	Isothipendyl	II
	R06AD52	Promethazine, combinations	III
R06AE	*Piperazine derivatives*		
	R06AE01	Buclizine	II
	R06AE05	Meclozine	II
	R06AE06	Oxatomide	II
	R06AE07	Cetirizine	II
	R06AE09	Levocetirizine	I

ATC	Substance Name		Category
R06AX	*Other antihistamines for systemic use*		
	R06AX02	Cyproheptadine	II
	R06AX07	Triprolidine	III
	R06AX09	Azatadine	II
	R06AX11	Astemizol	I
	R06AX12	Terfenadine	I
	R06AX13	Loratadine	I
	R06AX17	Ketotifen	II
	R06AX19	Azelastine	I
	R06AX22	Ebastine	I
	R06AX23	Pimethixene	II
	R06AX25	Mizolastine	II
	R06AX26	Fexofenadine	I
	R06AX27	Desloratidine	I
S Sensory Organs			
S01 Ophthalmologicals			
S01A	***Antiinfectives***		
S01AA	*Antibiotics*		
	S01AA02	Chlortetracycline	I
	S01AA04	Oxytetracycline	I
	S01AA11	Gentamicin	I
	S01AA12	Tobramycin	I
	S01AA16	Rifamycin	I
	S01AA20	Antibiotics in combination with other drugs	II
	S01AA30	Combinations of different antibiotics	I
S01AX	*Other antiinfectives*		
	S01AX13	Ciprofloxacin	I
		Thiomersal, combinations	II
S01B	***Antiinflammatory agents***		
S01BA	*Corticosteroids, plain*		
	S01BA01	Dexamethasone	I
	S01BA13	Rimexolone	I
S01BC	*Antiinflammatory agents, non-steroids*		
	S01BC01	Indometacin	I
	S01BC03	Diclofenac	I

ATC	Substance Name		Category
S01C	***Antiinflammatory agents and antiinfectives in combination***		
S01CA	*Corticosteroids and antiinfectives in combination*		
	S01CA01	Dexamethasone and antiinfectives	I
	S01CA03	Hydrocortisone and antiinfectives	I
	S01CA05	Betamethasone and antiinfectives	I
S01CC	*Antiinflammatory agents, non steroids and anti-infectives in combination*		
	S01CC01	Diclofenac and antiinfectives	I
S01E	***Antiglaucoma preparations and miotics***		
S01EA	*Sympathicomimetics in glaucoma treatment*		
	S01EA02	Dipivefrine	I
	S01EA03	Apraclonidine	I
	S01EA05	Brimonidine	I
S01EB	*Parasympathicomimetics*		
	S01EB01	Pilocarpine	II
	S01EB02	Carbachol	II
	S01EB08	Aceclidine	II
	S01EB09	Acetylcholine	II
	S01EB51	Pilocarpine, combinations	II
	S01EB58	Aceclidine, combinations	II
S01EC	*Carbonic anhydrase inhibitors*		
	S01EC03	Dorzolamide	I
	S01EC04	Brinzolamide	I
S01ED	*Beta blocking agents*		
	S01ED01	Timolol	II
	S01ED02	Betaxolol	I
	S01ED03	Levobunolol	I
	S01ED04	Metipranolol	I
	S01ED05	Carteolol	I
	S01ED06	Befunolol	I
	S01ED51	Timolol, combinations	II
S01EE	*Prostaglandin analogues*		
	S01EE01	Latanoprost	I
	S01EE03	Bimatoprost	I
	S01EE04	Travoprost	I

ATC	Substance Name		Category
S01F	***Mydriatics and cycloplegics***		
S01FA	*Anticholinergics*		
	S01FA01	Atropine	III
	S01FA04	Cyclopentolate	III
	S01FA05	Homatropine	III
	S01FA06	Tropicamide	III
	S01FA56	Tropicamide, combinations	III
		Hyoscyamine	III
S01FB	*Sympathicomimetics excl antiglaucoma preparations*		
	S01FB01	Phenylephrine	III
S01G	***Decongestants and antiallergics***		
S01GA	*Sympathicomimetics used as decongestants*		
	S01GA02	Tetryzoline	II
	S01GA05	Phenylephrine	II
	S01GA06	Oxedrine	II
	S01GA51	Naphazoline, combinations	II
	S01GA55	Phenylephrine, combinations	II
	S01GA56	Oxedrine, combinations	II
S01GX	*Other antiallergics*		
	S01GX01	Cromoglicic acid	I
	S01GX02	Levocabastine	I
	S01GX07	Azelastine	I
	S01GX08	Ketotifen	I
	S01GX09	Olopatadine	I
S01J	***Diagnostic agents***		
S01JA	*Colouring agents*		
	S01JA01	Fluorescein	I
S01XA	***Other ophthalmologicals***		
S01XA	*Other ophthalmologicals*		
		Boric acid	I
V Various			
V03 All Other Therapeutic Products			
V03A	***All other therapeutic products***		
V03AB	*Antidotes*		
	V03AB25	Flumazenil	I

Drugs, Driving and Traffic Safety
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Appendix II
International Council on Alcohol, Drugs and Traffic Safety. Guidelines on experimental studies undertaken to determine a medicinal drug's effect on driving or skills related to driving

Introduction

Importance of guidelines

Medicinal drugs are an integral part of almost all medical treatments. In relieving and curing diseases, they provide the population with a positive contribution to quality of life. Besides the beneficial effects, many commonly used medicinal drugs possess the potential for seriously impairing human performance. Concerning medicinal drugs and traffic safety, De Gier [1] states that a very conservative estimate indicates that 10% of the adult population drives under the influence of impairing drugs with twice the risk of being involved in a traffic accident and that, assuming this figure, those drugs are causing 4,500 deaths, 135,000 injuries and 6,3 billion EURO in property damage and immediate medical care each year in Europe.

Since epidemiological studies on the effects of medicaments are rare, the hazardous potential of medicinal drugs is hard to assess. Thus, findings of experimental studies on drugs and driver fitness are of great importance as the basis for decisions in the field of traffic safety. The empirical studies, as a whole, are suitable as a data base for categorizing the potential hazard of medicinal drugs only when they are based on a sound methodology and when the results of different studies are comparable. A review of the literature leaves the impression that these prerequisites are not met due to, among other things, the considerable variety of elements of the study design, of the sample choices, of the treatment, of the methods of testing driver fitness, and of the statistical evaluation. Due to these methodological differences and to many other reasons – for example economical ones, reasons of product safety, on the possibility of judging the quality of a study by sponsors of a study or authorities – a harmonization, optimization, and standardization of the experimental methodology is indispensable.

Activities of ICADTS and goal of the paper

The aforementioned shortcomings caused the scientific community in the field to select the methodology of experimental studies on medicinal drugs and driver fitness as a central theme in workshops and symposia. Systematic international efforts cosponsored by ICADTS began in 1991. On the basis of a paper and a questionnaire prepared by Vermeeren, De Gier and O'Hanlon, experts in the field discussed the appropriate questions at an International Workshop in Padova, 1991 [2]. The results of these discussions were published by De Gier and Laurell [3]. In addition, other experts answered the questionnaire, and the results were published as a final report containing guidelines with arguments by Vermeeren et al. [4, 5]. The efforts were followed by workshops and presentations of ICADTS Congresses in Cologne (T'92), Adelaide (T'95), and Annecy (T'97) and a Symposium in Nuremberg in 1994 (see [5]). Due to the relevance and the scope of the endeavor needed, and due to the fact that improvement of methodology is a constant task, the ICADTS established a Working Group on the topic in autumn 1994.

This paper completes the first task of the Working Group, namely to compile the guidelines concerning the adequate methodology of studies on drugs and driver fitness as discussed in the above mentioned papers and events.

This document is specifically addressed to pharmaceutical manufacturers and medicinal drug regulatory authorities who share the responsibility for ensuring the safe use of medicinal drugs by patients who operate motor vehicles. It is hoped that the material presented herein will lead to guidelines for the standardized assessment of each new medicinal drug's hazard potential for driving as part of the registration process. Programmatic research should lead in all cases to the categorization of the medicinal drug's hazard potential using a simple scheme that will be understood by the prescriber, dispensers, and ultimate users.

Even though the topic of illicit drugs may currently be attracting more attention than medicinal drugs, the guidelines at hand are restricted to medicinal drugs. The fundamental reason against the inclusion of illicit drugs is – in our opinion and probably in the opinion of all doctors prescribing medicinal drugs – the essential difference between medicinal drugs and illicit drugs. Medicinal drugs are necessary and valuable to patients to relieve and cure diseases. On the contrary, illicit drugs are not necessary and are detrimental to consumers. Therefore, all things should be avoided that combine medicinal drugs with illicit drugs. The important danger in establishing guidelines for medicinal drugs and illicit drugs simultaneously would be the trivialization of the problem of illicit drugs.

Introductory remarks to the compilation of the guidelines

It goes without saying that the established international and national guidelines relating to clinical, therapeutic experiments that can be adopted for research on drugs and driver fitness should be the basis of the recommended guidelines. For example: WHO and EC guidelines for good clinical research practice for trials on pharma-

ceutical products (WHO, EC), guidelines for the format and content of the clinical and statistical section of an application (FDA), biostatistical methodology in clinical trials in application for marketing authorization for medical products (EC) or structure and content of clinical study report (ICH) [6–10].

Hence, in the following we concentrate in essence on methodological aspects specific to empirical studies on medicinal drugs and driver fitness. Only those issues of the general guidelines are addressed that are often neglected and that have been found to be partially incomplete in the literature, but that are considered to be essential criteria for the quality of evaluation.

The following guidelines are based fundamentally on the papers of De Gier and Laurell [3] and Vermeeren et al. [4]. A completion was done by Berghaus and Friedel [11, 12], the results of the discussion of the Workshop in Cologne, the Symposium in Nuremberg, and the ICADTS Working Group Meetings in Adelaide and Annecy.

Besides this brief summary of guidelines, a more detailed one with comments to and references of the particular propositions has been established (ICADTS) [13].

We would like to point out that the guidelines recommended are not intended to restrict research on a few established methods but to provide the investigator with a minimum set of quality assured, acceptable guidelines. The researcher is encouraged to include new elements (such as new tests, variables or measurement methods) in order to further develop methodological and psychological knowledge and to obtain a complete differential profile of the medicinal drug effects. The aim, objectives, and methods of the study should be described in advance in a detailed study protocol. Herein, the investigator should give arguments for the use of methods that differ from the suggestions of these guidelines.

Hypothesis and sample size

Hypothesis

Investigators should state their hypothesis concerning a particular medicinal drug's effect before starting the study. They should distinguish clearly between the following hypotheses:

– *Testing for "difference":*
  The drug is assumed to have an effect on performance different from the effect of placebo or some other drug.
– *Testing for "equivalence":*
  The drug is assumed, a *priori*, to have an effect on performance equivalent to that of placebo or some other drug.

It is quite common to consider driver unfitness as an adverse drug effect. In this sense the decision problem is an equivalence rather than a difference testing problem. However, in both cases it is common sense to choose the probability of an

erroneous rejection of the hypothesis (type one error probability, denoted by α) at 5% and to make sure that the probability of erroneously accepting the hypothesis (type two error probability, denoted by ß) does not exceed a moderate level (10–20%). Hereby, the test procedure is usually based on two-sided hypotheses. Note that if the intention is to test for difference and it results in a non-significant result, then it is not correct to decide for equivalence. There are various methods to test for equivalence, such as test procedures and confidence interval inclusion rules developed in the area of bioequivalence [14]. For the equivalence testing problem, one also has to specify the tolerance region or equivalence region which corresponds to the (minimal) relevant difference. The tolerance region may be bounded by the maximal tolerable degree of driving hazard potential.

Sample size

The sample size should be based on power calculations. In the study protocol, reasons following statistical arguments with respect to the design chosen, the analysis procedure (e.g. multiple comparison procedures, equivalence tests etc.), and the predetermined type one and type two error probabilities should be given to insure the feasibility of the sample size to test the hypotheses under investigation. Usually type one and type two probabilities are fixed in advance, and the sample size is selected subject to the relevant difference to be tested.

Subjects

Representativeness, healthy volunteers *versus* patients

The subject sample should be representative (at least with respect to age and gender) of the driving population and the target population of the drug. Subjects should especially have adequate driver experience measured, for example, by minimum annual mileage or minimum overall mileage.

The individuals participating as volunteers in a study may be either healthy or patients. A program of drug assessment should generally start with healthy volunteers. A patient study should follow if different effects concerning performance between healthy volunteers and patients are assumed.

Exclusion criteria

Subjects with hearing or visual deficits (esp. color blindness), alcohol, medicines, drug abuse or addiction, and other factors known to affect performance must be excluded; moreover subjects who are expected (from any genetic or other predisposition) to either not respond or respond differently or adversely to the medicinal

drug must not be included. In addition to the normal selection procedures for any subject that involve medical history screening and routine physical examination, extra precaution should be taken for middle aged and elderly subjects in the form of additional medical screening (e.g. blood and urine chemistry, hematological examinations, resting ECGs). Medical screening of female subjects should include a pregnancy test before beginning the trial, and assurance of reliable birth control should be provided during trial.

The above mentioned selection criteria should be controlled as far as possible by objective tests. For example, a physical examination including the screening of a blood/urine specimen concerning alcoholism indicators should be used instead of only using questionnaires about alcohol addiction.

Design and treatment

General aspects of the design

Cross-over designs reduce the variance of the treatment contrast (if carry-over effects are negligible) and are, therefore, to be preferred for efficiency. In most cases the power is maximized compared to the parallel group design, which leads to a smaller sample size but is often impossible to use in patient studies or in studies with slowly eliminated drugs (carry-over effect). In such cases parallel group designs are necessary.

In addition to the general exclusion criteria for subjects, alcohol and illicit drug use and concomitant medication, except oral contraception, overtiredness and other factors known to influence performance must be checked and/or controlled each test day before starting the test procedures in order to be able to describe the homogeneity of the intra-individual trial conditions of each subject.

Apart from the test procedures chosen as operationalization of driver fitness (see below), additional elements should be included in a test day. Suitable specimens (blood, plasma, urine, saliva) should be taken for checking the compliance with the test conditions and for measuring pharmacokinetic quantities of the test medication. Tests and/or a questionnaire concerning the subjective feelings of the subjects with respect to sedation, experienced performance impairment, impression on driver fitness, and willingness to drive, for example have to be included. These tests must fulfill the same objective quality criteria as the performance tests.

Control conditions

Studies on investigational drugs generally should include the following control conditions:

– *placebo*
– *verum.*

The standard active drug (verum) serves as a positive control that should demonstrate the sensitivity of the experimental procedure. Studies including the use of a verum should preferably use one of the following: an impairing representative of the same therapeutic class; ethanol sufficient to raise blood alcohol concentration (BAC) to 0.5 or 0.8 mg/ml; or diazepam 10 mg. If the use of a placebo or verum is thought to be not necessary, this should be explained.

Treatment

Studies undertaken to demonstrate the effect of a new medicinal drug on driver fitness should involve at least the lowest and highest dose to be given therapeutically; or at least 1 × and 2 × the dose, if there is only one therapeutic dose recommended. Wherever possible, a drug should be tested additionally in healthy volunteers in doses of 4 × the standard therapeutic dosage (if the drug is well tolerated in this dosage) to establish a dose-effect curve.

Concerning treatment duration, a study should last at least until a steady state of the drug plasma concentration has been achieved, or until the desired therapeutic effect has occurred in patients.

In cross-over designs the wash-out phase must be long enough to exclude carry-over effects and should be defined according to the pharmacodynamic properties of the substance (in general, four or five times the drug's half-life). The rationale of the decision should be made clear.

Pharmacokinetic and -dynamic interactions between medicinal drugs commonly used in combination and interactions between alcohol and medicinal drugs should be considered. Assessment of the effects of those combinations on performance should always be conducted when it is definitely known that the presence of one interferes with the metabolism of the other; or, when both possess independent mechanisms of action causing impairment so that the possibility of a synergistic (i.e., multiplicative) effect exists.

Operationalization of driver fitness

Kind of operationalization

Studies for establishing the driving hazard potential of a particular medicinal drug should proceed from conventional laboratory testing to sophisticated driving simulators. Finally, actual driving tests (over-the-road tests in normal traffic conditions or tests on closed circuits under controlled conditions) should be carried out as far as they can safely be applied and will be allowed by the ethics commission. The final evidence that the drug in question would be safe or hazardous to a specified degree should be based on the combined results of all tests in the program. Combining the results from programmatic research should follow scientific guidelines.

Laboratory tests

Test batteries

A performance test battery as a sound operationalization of the construct "driver fitness" should possess content validity. That means, the test battery as a whole should be representative of the mental and/or behavioral functions relevant to driving and, simultaneously, should be representative of the pharmacological effects of the drug under study.

Concerning the elements of the test battery, studies should include a test to measure divided attention or continuous perceptual-motor coordination and a test to measure sedation or drowsiness. Furthermore, the test battery should comprise performance areas like discrete perceptual motor response, speed and accuracy of decision making, sustained attention (vigilance), dynamic visual acuity, short-term spatial memory, risk avoidance and attentional resistance to distraction. This list is not closed.

The duration of the test battery will depend on, among other things, the kind and number of tests included, the medicinal drug, and the question of whether a time course effect should be studied. There should be at least one test in the battery of longer duration (e.g. one hour).

Individual tests

Many representative test procedures exist to test a single mental and/or behavioral function. The choice of an adequate test is left to the investigator who should choose a standard procedure or, if using a new one, the investigator should demonstrate that the procedure is able to discover the impairment addressed by the mental and/or behavioral function under study. In any case, the test selected must meet the requirements outlined in the following.

Performance tests included in a test battery should possess construct validity. That means that the measures of the tests should be simultaneously relevant to driving performance and sensitive to the pharmacological drug effects.

A validation of medicinal drug-induced changes in performance with changes in actual driving performance should be made before using laboratory tests in categorization procedures or other legal/regulatory affairs. Laboratory tests should possess either a test-retest reliability coefficient for raw scores measured in the absence of drug effects of $r >= .70$ or, preferably, a test-retest reliability coefficient for drug-placebo change scores of $r >= .50$.

A standardization of the measurement procedure of the dependent variables of a test is very important due to reasons of comparability between studies. The training of the subjects on the test should be continued to individual stability of performance (determined by group means, standard deviation, and intertrial correlations).

Simulators and real driving

The term "simulator" contains a wide range of constructions from very simple to highly sophisticated devices. Independent of the complexity, they should include tests of reactions to traffic signals, compliance with traffic control devices, passing maneuvers, and turning of intersections.

A similar state of affairs is valid for real driving. Independent of the variety of designing the procedure, closed-course driving should include decision-making, responses to changes in traffic control devices, and interactions with other experimentally controlled road users. Over-the-road driving tests have to include combined city and highway driving tests. The fundamental aspects of the driver-vehicle-road interaction (e.g. road tracking, speed maintenance, car following, etc.) have to be involved. The ethical implications must be considered with great care.

Statistical evaluation

General aspects

Standard aspects of the statistical evaluation should be followed. In general, the statistical methods must be described in advance. The description should include remarks on how to proceed with missing values, drop-outs, and extreme values during the analysis. The researcher should employ the most powerful statistical test that can rightfully be applied.

Comparisons among treatments at baseline may reveal the existence of carry-over effects in cross-over studies or differences among groups in parallel group design, thus justifying the use of difference values with respect to the baseline in the statistical analysis.

Use of a common scale

The performance measures should be recorded on a common scale for all psychometric tests. Most of the statistical procedures available for achieving this depend on population distribution parameters. Hence, investigators should gather these data in a central repository so that all investigators may use the information.

Multiple comparisons *versus* techniques of multiple endpoints

In general, the statistical evaluation is based on several dependent variables which represent different aspects of driver fitness. Therefore, the question is: how to reduce the results (items, endpoints) of the many dependent variables to one decision on driver fitness.

It is obvious that if one is interested in several dependent variables and performs independent tests at a given significance level without significance level adjustment, the probability of an erroneous decision for effect exceeds the given level dramatically. Hence, if several dependent variables are tested separately the α-inflation has to be taken into account. Investigators should indicate what measures they have taken to correct for α-inflation.

Instead of using the method of multiple comparisons, more use should be made of the newer techniques of "multiple endpoints" or "accumulation statistics" in which several dependent variables (i.e. several aspects of driver fitness) are synopsized. After having compared multiple dependent variables (summation of weighted z-scores; technique of "multiple endpoints") or computed a score as weighted (weights defined a priori by the scientific community according to the importance of the skills to driver fitness, technique of "accumulation statistics"), a t-test for equivalence hypothesis is performed [15–18].

Interpretation

The interpretation of the results should start with an a priori definition of a practically relevant change in performance. An alteration in performance of at least one population standard deviation should be interpreted as a relevant change in performance. The interpretation should result in categorizing a drug as "presumed to be safe or unlikely to produce an effect", "likely to produce minor or moderate effects", or "likely to produce severe adverse effects or presumed to be potentially dangerous" according to the 3-tier warning system for identifying the driving hazard potential of a drug as part of the pan-European registration process accepted by the European Committee for Proprietary and Medicinal Products (CPMP).

Publication of results

An exhaustive description of the material, methods and results is most important due to reasons of scientific precision and due to the growing importance of meta-analyses. Appropriate guidelines are to be found in almost all scientific journals.

With respect to experimental studies on drugs and driver fitness, a precise description of inclusion and exclusion criteria for subjects (i.e., the diseases and addictions checked and the examinations used) and of the methods used to exclude performance influencing factors other than the treatment under study is necessary.

To avoid publishing bias, it is very important to report on all studies even if no consistent results (i.e. in comparison with the results of other studies) are obtained.

In each study report, the design and the statistical analysis should be described by the α -risk (including the method to correct for α-inflation), the ß-risk, the effect size, the sample size, the number of outliers and drop-outs, and the decision criteria to select them, mean values, standard deviations, the analysis of variance table if

used or other statistical results, and the statistical package. Reasons for the selection of statistical tests should be given, and it should be demonstrated that the assumptions to use a specific statistical test are fulfilled.

The data exchange should be improved by providing disks with raw data to other researchers on request.

Concluding remarks

The compendium provides a basis for establishing desirable criteria concerning the experimental methodology of research into the field of medicinal drugs and driver fitness. The guidelines arranged will form the basis for further exploration of how the scientific community looks upon these issues. This intention has many implications.

1. It was not to be expected that all participants of the Workshops and the Working Group would achieve total agreement on the propositions presented in this paper. Differences in opinion are largely attributable to the variety of methods used to investigate the effects of medicinal drugs on driver fitness.
2. The compendium is not to be regarded as complete and all-inclusive. Some investigators will judge that one or other proposition is self-evident whereas other researchers would like to have some propositions more detailed or more scientifically based.
3. Another aspect is the fact that the desirable may not always be achievable. Reasons may include, for example, the prescribed length of a project or the group of subjects investigated, which is limited in quantitative terms. Surely in such cases the investigator should carry out the research, but should indicate why it was impossible to follow the proposals.
4. Further research on experimental methods will be necessary. As a central issue, we would like to point out the development of a sound theory of driver fitness including the establishment of a requirement profile concerning safe driving. Based on this theory, it should be possible to formulate detailed guidelines for simulator and on-the-road tests and to rank mental and/or behavioral functions according to their importance.

Final practical application of the guidelines, however, will require additional concerted action and development by the parties involved: researchers, psychopharmacological research organizations and institutes, the pharmaceutical industry, and regulatory authorities.

In conclusion, we would like to recall that these guidelines should not restrict research, but they should support a movement towards optimizing, harmonizing, and standardizing experimental procedures for assessing the adverse effects of medicinal drugs on driving performance.

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