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Effects of Benzodiazepines, Antidepressants and Opioids on Driving

A Systematic Review and Meta-Analysis of Epidemiological and Experimental Evidence

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Abstract

Background: Many individuals in the community are prescribed psychoactive drugs with sedative effects. These drugs may affect their daily functions, of which automobile driving is a major component.

Objective: To examine the association of three classes of commonly used psychoactive drugs (*viz*. benzodiazepines and newer non-benzodiazepine hypnotics, antidepressants and opioids) with (i) the risk of traffic accidents (as indexed by epidemiological indicators of risk); and (ii) driving performance (as indexed by experimental measures of driving performance).

Methods: A literature search for material published in the English language between January 1966 and January 2010 in PubMed and EMBASE databases was combined with a search for other relevant material referenced in the retrieved articles. Retrieved articles were systematically reviewed, carrying out meta-analyses where possible. Twenty-one epidemiological studies (13 case-control and 8 cohort studies) fulfilled the inclusion criteria by estimating the accident risk associated with drug exposure (ascertained by blood/urine analysis or prescription records). Sixty-nine experimental studies fulfilled the inclusion criteria by testing actual or simulated driving performance after administering a single dose or multiple doses.

Results: Two meta-analyses showed that benzodiazepines are associated with a 60% (for case-control studies: pooled odds ratio [OR] 1.59; 95% CI 1.10, 2.31) to 80% (for cohort studies: pooled incidence rate ratio 1.81; 95% CI 1.35, 2.43) increase in the risk of traffic accidents and a 40% (pooled OR 1.41; 95% CI 1.03, 1.94) increase in 'accident responsibility'. Co-ingestion of benzodiazepines and alcohol was associated with a 7.7-fold increase in the accident risk (pooled OR 7.69; 95% CI 4.33, 13.65). Subgroup analysis of

case-control studies showed a lower benzodiazepine-associated accident risk in elderly (>65 years of age) drivers (pooled OR 1.13; 95% CI 0.97, 1.31) than in drivers <65 years of age (pooled OR 2.21; 95% CI 1.31, 3.73), a result consistent with age-stratified risk differences reported in cohort studies. Anxiolytics, taken in single or multiple doses during the daytime, impaired driving performance independent of their half-lives. With hypnotics, converging evidence from experimental and epidemiological studies indicates that diazepam, flurazepam, flunitrazepam, nitrazepam and the short half-life non-benzodiazepine hypnotic zopiclone significantly impair driving, at least during the first 2–4 weeks of treatment. The accident risk was higher in the elderly (>65 years of age) who use tricyclic antidepressants (TCAs); however, the evidence for an association of antidepressants with accident risk in younger drivers was equivocal. Sedative but not non-sedative antidepressants were found to cause short-term impairment of several measures of driving performance. Limited epidemiological research reported that opioids may be associated with increased accident risk in the first few weeks of treatment.

Conclusions: Benzodiazepine use was associated with a significant increase in the risk of traffic accidents and responsibility of drivers for accidents. The association was more pronounced in the younger drivers. The accident risk was markedly increased by co-ingestion of alcohol. Driving impairment was generally related to plasma half-lives of hypnotics, but with notable exceptions. Anxiolytics, with daytime dosing, impaired driving independent of their half-lives. TCAs appeared to be associated with increased accident risk, at least in the elderly, and caused short-term impairment in driving performance. Opioid users may be at a higher risk of traffic accidents; however, experimental evidence is limited on their effects on driving.

Background

Many individuals in the community are prescribed psychoactive drugs with sedative effects, such as benzodiazepines, tricyclic antidepressants (TCAs) and opioids. The vast majority of those who are treated with these drugs are outpatients and are expected to carry out their daily activities in a similar manner to other individuals. However, these drugs can adversely affect the cognitive and psychomotor functions underlying daily activities, and some of those functions (e.g. reaction time, attention, visuospatial skills) are considered important in automobile driving.[1-3]

The effects of drugs on driving safety have been previously examined using epidemiological and experimental study designs. The epidemiological studies examine this relationship in terms of traffic safety by measuring the association between use of sedative psychotropic drugs and the risk of traffic accidents, while experimental studies approach the question by examining whether administration of drugs is likely to impair driving performance. The focus of the present review is to explore the role of three classes of psychoactive drugs (*viz*. benzodiazepines and newer non-benzodiazepine hypnotics, antidepressants and opioids) in traffic safety by combining the evidence from epidemiological and experimental studies, because each type of study in isolation fails to establish drugs as a causative factor in traffic accidents.

The outcome of interest in epidemiological studies is traffic accidents (in most instances injurious or fatal accidents), which are a major

outcome of immediate practical significance. Being observational studies, they fall short of establishing a cause and effect relationship between drug use and traffic accidents, i.e. detection of a drug in a driver who met with an accident does not necessarily mean that the drug was a cause for the accident.[4] Accident responsibility studies attempt to overcome this limitation by establishing that the drug in question is more prevalent in drivers responsible for accidents than in those who are not responsible for accidents. Therefore, the present review also focuses on accident responsibility studies.

The aim of experimental studies is to determine the effect of a single or a few doses of drugs on driving performance, as tested in different actual driving tests[5-7] or driving simulator tests.[8-10] Experimental studies can eliminate many of the limitations of epidemiological studies, but mostly at the cost of compromising the ecological validity. Driving performance is frequently tested in a highly controlled environment where only certain components of driving behaviour are examined through specific driving tasks. Certain driving tests however have achieved a greater ecological validity within a controlled environment and have also been validated against surrogate markers of traffic safety. For example, in a standardized driving test developed by O'Hanlon[5] in the early 1980s, the primary outcome measure is the driver's ability to maintain the lateral position of the vehicle in the driving lane. Cognitive models of driving define such processes as 'operational' processes of driving, which are necessary for stable driving.[11-13] The degree of weaving of the vehicle (termed standard deviation of lateral position [SDLP]) was calibrated against different blood levels of alcohol, which is a known risk factor for traffic accidents.[5] Several recent reviews have comprehensively analysed the effects of different doses of commonly used benzodiazepine and non-benzodiazepine hypnotics[14,15] and antidepressants[16] on this measure of lateral position control in highway driving. While impaired performance in the above driving test suggests the participant is unfit for highway driving, unimpaired driving performance does not necessarily mean that one is able to drive safely, particularly in complex driving environments where the driver has to respond to other vehicles, pedestrians, traffic signs and other roadside objects. According to cognitive models of driving, more complex processes that are necessary to interact with the external environment and to help make higher level decisions in driving are categorized as 'tactical' and 'strategic' level processes.[11-13] Different actual and simulated driving tests have been used to tap these higher level aspects of driving and are reviewed in the present paper.

Many recent epidemiological studies[17-19] and reviews of experimental studies[14-16] emphasize the differences in the effects of individual drugs (even if they are in the same class of drugs). Accordingly, the present review will also focus on the level of individual drugs. In addition, we also focus on different subject factors (patients vs healthy volunteers, young vs the elderly) that are likely to modify drug effects on driving and traffic accidents.

The broad objective of the present study was to systematically review the literature to find out whether three groups of commonly used psychoactive drugs (benzodiazepines and newer non-benzodiazepine hypnotics, antidepressants and opioids) are associated with increased risk of traffic accidents and impaired driving. More specifically, we aimed to examine (i) whether use of each of these drugs is associated with increased risk of traffic accidents (as indexed by risk estimates measured in analytical epidemiological studies); and (ii) whether experimental administration of these drugs causes impairment in driving performance (as indexed by quantitative measures of driving performance in an actual vehicle or a driving simulator).

Methodology

Literature Search Strategy

We conducted a literature search on the PubMed and EMBASE databases for material published between January 1966 and 31 January 2010. The search was limited to human studies published in English. Two sets of search terms were used. The first set consisted of the EMTREE/MeSH terms 'benzodiazepine derivative', 'zaleplon', 'zopiclone', 'zolpidem', 'zolpidem tartrate', 'eszopiclone' (i.e. 'z drugs'), 'antidepressant agent' and 'opiate agonist'. The

second set included the EMTREE/MeSH terms 'traffic accidents', 'traffic safety' and 'car driving' and the general search term 'driving'. By selecting the 'explosion' option, the search also incorporated the terms that are subtopics (e.g. individual drugs in a particular class of drugs) of each of the above EMTREE/MeSH terms. The articles that contained at least one term from each of the above sets of search terms were extracted for consideration for inclusion in the review. The reference lists of the eligible articles were searched for any other relevant literature.

Inclusion Criteria

Inclusion criteria for epidemiological studies were (i) cohort or case-control study design or variants such as case-crossover studies (survey designs and other descriptive studies were excluded); and (ii) explicitly stated exposure ascertainment (e.g. detection of drugs in body fluids, records of drug prescription) and outcome ascertainment (i.e. traffic accidents or subcategories such as 'traffic accidents required hospitalization' or 'fatal traffic accidents'). The research methods of epidemiological studies were assessed based on the appropriate fields outlined in STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statements for case-control studies and cohort studies.

The inclusion criteria for experimental studies were (i) administration of a single dose or multiple doses of a relevant drug to at least one of the study groups; and (ii) implementation of an actual driving test or a test in a driving simulator (studies that examined cognitive/psychomotor functions related to driving by laboratory tests were excluded). The methodology of the experimental studies was evaluated under four categories: experimental design, selection of study samples, pharmacological manipulation and outcome measures.

Meta-Analysis

The retrieved epidemiological studies were pooled for meta-analyses in the instances where adequate numbers of studies with required data were available. A random-effects model analysis (DerSimonian-Laird method) was employed to calculate the pooled estimates as it does not assume that each component study of the meta-analysis is derived from the same population, and hence allowed pooling statistically heterogeneous studies without compromising the statistical validity of the results. However, random-effects modelling generated wider confidence intervals (CIs) for the pooled estimate than fixed-effects modelling would do, thus compromising the precision of the pooled estimate. Subgroup analyses were planned in the instances where there was a severe statistical heterogeneity. However, this could be carried out only for the case-control studies on benzodiazepines (based on age), because there were too few studies in the other meta-analyses.

Results

The initial search retrieved 1271 articles. Exclusion of the papers that did not meet the inclusion criteria are summarized in figure 1. This initial literature search retrieved 15 epidemiological studies and 54 articles on experimental studies. A review of the reference lists produced an additional 6 epidemiological studies and 9 experimental studies. Thus, in total, 21 epidemiological studies and 69 experimental studies (in 62 papers) met the aforementioned inclusion criteria. Of the 21 epidemiological studies, 13 were case-control studies (table I) and 8 were cohort studies (table II). Nineteen epidemiological studies investigated exposure to benzodiazepines, 6 to antidepressants and 7 to opioids. Of the 69 experimental studies, benzodiazepines and/or 'z drugs' (see section 2.1 for definition and list) were tested in 48 studies (see supplementary table 1, Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A37), antidepressants in 20 studies (supplementary table 2, Supplemental Digital Content) and opioids in three studies (supplementary table 3, Supplemental Digital Content).

Epidemiological Studies: Risk of Traffic Accidents and Use of Benzodiazepines, Antidepressants and Opioids

The methodology and results of 13 case-control studies and 8 cohort-studies are summar-

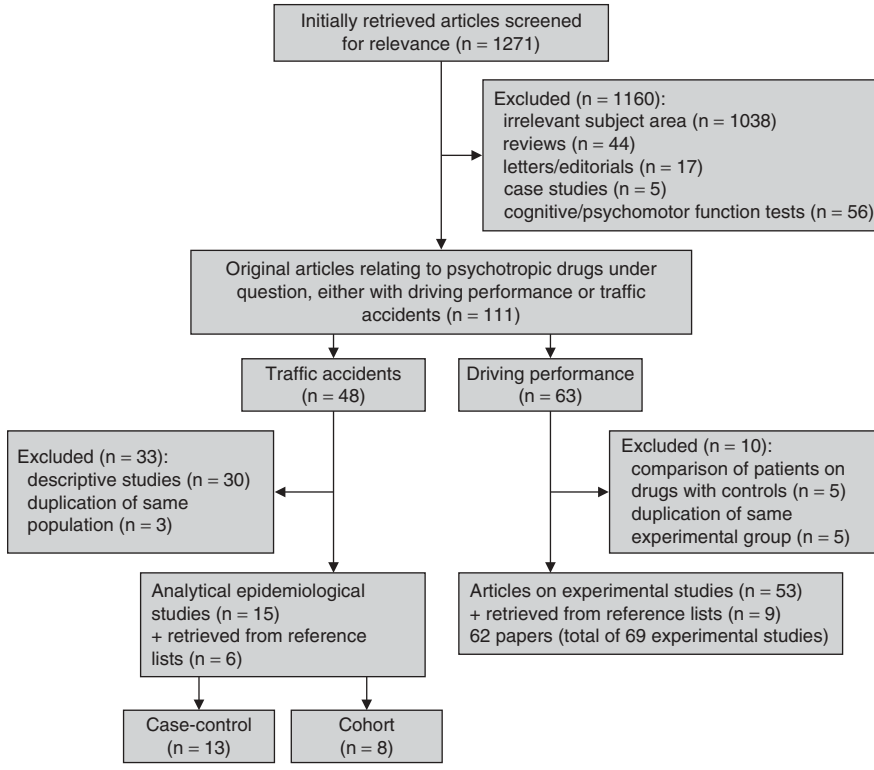

Fig. 1. Selection process of studies.

ized, with the limitations specific to individual studies noted in tables I and II, respectively.

Two distinct sampling methods can be observed in epidemiological studies. Seven case-control studies 'recruited' cases from drivers who were hospitalized[4,21,23,29,31] or died[32,39] after traffic accidents, whereas controls were victims of traffic accidents selected from the scene of accidents or individuals selected randomly at fuel stations or roadside.[21,31] Drug exposure was ascertained by analysing the blood or urine samples. The main advantage of this method is the availability of confirmatory evidence for the presence of the drug under question at the time of accident.

In other case-control studies (except one, where exposure was ascertained through an interview[28]) and all cohort studies, both exposure and outcome ascertainment was registry-based. Accident involvement was ascertained from entries in hospital admission or general practice databases or road accident registries, and drug exposure was ascertained by means of prescription entries in drug prescription databases. Outcome ascertainment was based on motor registry data or medical records. The number of days for which the drugs are prescribed was usually considered the 'exposed period'. Linkage of the two databases showed whether the patient was prescribed (and hence likely to be taking) the drugs at the time of the accident. The advantage of this approach is the ability to enlist large numbers of subjects, thus increasing the power of the study.

However, this registry-based approach has also introduced certain biases common to many of these observational studies. First, it introduces an exposure ascertainment bias. It is impossible to know whether patients had been actually taking the prescribed drugs during the designated 'exposed period' and had not been taking any

Table I. Case-control studies on the effects of benzodiazepines (BDZs), antidepressants and opioids on the risk of road traffic accidents (TAs)

Study (y; country)	Design (period)	Study population from which samples selected	Cases	Controls	Drug exposure ascertainment	Adjustment/stratification/ controlled/variables	Subgroups/studied drug groups	Results: risk measure (95% CI)	Comments/consideration
Skegg et al.[20] (1979; UK)	Matched (Mar 1974–Feb 1976)	43 117 people registered with 16 GPs	57 drivers who died or were hospitalized due to injuries from TA	1425 randomly selected people from GP registers	Prescription records: prescribed and dispensed with a tranquillizer within 12 wk before TA	Matched for sex, general practice enrolled, year of birth	All tranquillizers Minor tranquillizers Major tranquillizers	RR 5.2 (2.2, 12.6) RR 4.9 (1.8, 13.0) RR 6.9	No CI given for major tranquillizers as there were too few subjects
Honkanen et al.[21] (1980; Finland)	(Apr, May, Sep, Oct 1977)	Injured car drivers arriving at EDs in Helsinki	201 drivers arrived at ED within 6 h after TA	325 car drivers selected randomly at petrol stations	Serum analysis for BDZs	Matched for weekday, hour of day and location of accident	BDZs (mainly diazepam)	More commonly detected in cases than in controls ($p < 0.03$)	May have introduced a bias as the duration of holding the licence was shorter and blood alcohol levels higher in cases than controls
Jick et al.[22] (1981; USA)	(Jan 1977–Dec 1978)	Patients (15–64 y) discharged from a Group Health Corporative hospital with diagnosis of injury due to automobile accident	93 drivers 'at fault' of the accident, as recorded in clinical notes	Group 1: 63 passengers Group 2: 85, driver-status undetermined (45), not-at-fault drivers (13), drivers' fault status unknown (27)	Prescription records: at least one prescription for sedative drug (major or minor tranquillizer, antihistamines or opioid analgesic) within 3 mo of accident	Matched for sex	At-fault drivers vs passengers (for use of any drug group)	Crude OR 1.0 Sex-adjusted OR 1.1 (0.6, 2.2)	Not included in meta-analysis because of (i) questionable accuracy of clinical notes in assigning at-fault status of drivers; (ii) no adjustment for alcohol (more cases drinking than controls); (iii) no direct comparison of drivers at fault and not at fault
Lagier[23] (1993; France)	(May 1989–Jul 1990)	Patients admitted to hospital after TA injury	Drivers responsible for accident	Drivers not responsible for accidents and pedestrians	Blood analysis for BDZs		Blood alcohol <0.2 g/L Blood alcohol >0.2 g/L Blood alcohol 0.2–0.8 g/L with no BDZs	OR 0.96 (0.8, 1.2) OR 7.2 (3.4, 15.2) OR 2.03 (1.4, 2.9)	BDZ-alcohol combination increases risk compared with alcohol/BDZ alone
Leveille et al.[24] (1994; USA)	Matched (1987–8)	Enrollees of Group Health Corporative, Puget Sound	234 drivers aged >65 y sought treatment for TA within 7 days of	447 drivers >65 y matched for age, sex and county of residence, but not met with	Prescription records Current exposure: prescription within 60 days	Race, marital status, education, miles driven, insulin or oral hypoglycaemic use for diabetes mellitus	*BDZs:* current exposure past exposure	 OR 0.9 (0.4, 2.0) OR 1.2 (0.5, 2.7)	Main BDZ triazolam (~50%) Exposure status was defined in relation to a given class of drugs. 'Unexposed group'

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Table I. Contd

Study (y; country)	Design (period)	Study population from which samples selected	Cases	Controls	Drug exposure ascertainment	Adjustment/stratification/ controlled/variables	Subgroups/studied drug groups	Results: risk measure (95% CI)	Comments/consideration
			accident	TA during the same calendar year	Past exposure: prescription 60 days–6 mo before No exposure: no prescriptions within 6 mo		*Cyclic antidepressants:*		may have been exposed to another class of drug; thus the OR may underestimate actual risk. Risk of being 'at-fault' for accidents was also higher in those exposed to drugs
							current exposure	OR 2.3 (1.1, 4.8)	
							past exposure	OR 0.7 (0.2, 1.9)	
							Opioids:		
							current exposure	OR 1.8 (1.0, 3.4)	
							past exposure	OR 1.0 (0.5, 1.8)	
							No. of drugs in current users		
							1 type	OR 1.3 (0.8, 2.0)	
							≥2 types	OR 2.0 (1.0, 4.0)	
Hemmelgarn et al.[25] (1997; Canada)	Nested (Jun 1990–May 1993)	Subjects aged 67–84 y who possessed a valid driving licence and resided in Quebec for at least 2 y	5579 drivers involved in injurious crashes	55 790 drivers (10 per one case) who were at risk of but did not meet with accidents during the index date	Prescription records: exposed if index date included the period of prescription, not exposed if no BDZ use within 365 days preceding index date	Sex, age, locality of residence, history of previous injurious TA, chronic disease score, use of other CNS drugs	*Long $t_{1/2}$ BDZs:*		Long $t_{1/2}$: clonazepam, diazepam, clorazepate, flurazepam, nitrazepam, chlordiazepoxide
							current use	OR 1.28 (1.12, 1.45)	
							first week of use	OR 1.45 (1.04, 2.03) OR remains high in first year of use	
							Short $t_{1/2}$ BDZs:		Short $t_{1/2}$: alprazolam, bromazepam, lorazepam, oxazepam, temazepam, triazolam
							current use	OR 0.96 (0.88, 1.05)	
							first week of use	OR 1.04 (0.81, 1.34)	

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Table I. Contd

Study (y; country)	Design (period)	Study population from which samples selected	Cases	Controls	Drug exposure ascertainment	Adjustment/stratification/ controlled/variables	Subgroups/studied drug groups	Results: risk measure (95% CI)	Comments/consideration
Barbone et al.[26] (1998; UK)	Case-crossover (Jan 1992–Jan 1995)	410 306 residents in Tayside region, UK, who had been registered with a Tayside GP	19 386 persons ≥18 y who experienced a TA Case period: the day of TA	Control period: same day of the wk in preceding 18 wk	Intake of the drug on the day based on dispensed prescription records	Stratified for age, sex, severity of injury, breath alcohol, lighting, driver culpability	*BDZs:*		Drivers taking BDZs are more likely to be responsible for TAs. ORs for BDZs decrease with age Anxiolytics: alprazolam, bromazepam, diazepam, lorazepam, chlordiazepoxide, clorazepate, oxazepam Hypnotics: flunitrazepam, flurazepam, loprazolam, lormetazepam, nitrazepam, temazepam
							all	OR 1.62 (1.24, 2.12), higher risk with higher doses and alcohol co-ingestion	
							anxiolytics	OR 2.18 (1.52, 3.13), dose-related increase in risk	
							hypnotics	OR 1.19 (0.83, 1.70)	
							zopiclone	OR 4.00 (1.31, 12.2)	
							TCAs	OR 0.93 (0.72, 1.21)	
							SSRIs	OR 0.85 (0.55, 1.33)	
Longo et al.[4] (2000; Australia)	(Apr 1995–Aug 1996)	2500 injured drivers from SA	Drivers culpable for TA	Drivers not culpable for TA	Detection of drugs in blood samples	Stratified for different drug concentrations in blood	*BDZs alone:*		CIs for ORs not given. These findings are also presented in Longo et al.[27] (2001), with emphasis on BDZs. The results are similar
							all levels	OR 2.0 [$p < 0.05$]	
							subtherapeutic	OR 1.3 [$p > 0.05$]	
							therapeutic	OR 3.3 [$p < 0.05$]	
							supratherapeutic	OR 3.6 [$p < 0.05$]	

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Table I. Contd

Study (y; country)	Design (period)	Study population from which samples selected	Cases	Controls	Drug exposure ascertainment	Adjustment/stratification/ controlled/variables	Subgroups/studied drug groups	Results: risk measure (95% CI)	Comments/consideration
							BDZs + alcohol:	OR 13.4 [$p < 0.05$]	
McGwin et al.[28] (2000; USA)	(Jan–Dec 1996)	39 687 residents of Mobile County, AL, ≥65 y who had a driver's license in 1996	244 at-fault drivers involved in TAs from 1 Jan 1996 to 31 Dec 1996	1. 182 not-at-fault drivers involved in crashes during same period 2. 475 drivers not involved in crashes	Self-reporting of medication use in a telephone interview	Age, sex, mileage of driving	*BDZs:* at-fault drivers vs drivers not involved in TA at-fault vs not-at-fault drivers *Antidepressants:* at-fault drivers vs drivers not involved in TA at-fault vs not-at-fault drivers	 OR 5.2 (0.9, 30.0) OR 1.0 (0.2, 4.6) OR 0.8 (0.2, 3.0) OR 1.3 (0.2, 6.7)	Whether the subjects were taking medication during the time of accident is not specified
Mura et al.[29] (2003; France)	(Jun 2000–Sep 2001)	Patients >18 y admitted to EDs	900 drivers after TAs	900 patients admitted due to other reasons	Detection of drugs in blood samples	Matched for age, sex	BDZs only	OR 1.7 (1.2, 2.4)	
Drummer et al.[30] (2004; Australia)	1990–9: (variable periods in different states)	Drivers killed in TAs in VIC, NSW and WA	Drivers culpable for crashes	Drivers not culpable for crashes	Detection of drugs in blood samples	Age, sex, no. of vehicles in crash, state, year of crash	BDZs only Opioids only	OR 1.27 (0.5, 3.3) OR 1.41 (0.7, 2.9)	Only fatal crashes were analysed. Small sample sizes
Movig et al.[31] (2004; Netherlands)	(May 2000–Aug 2001)	Injured and non-accident-involved drivers in Tilburg	110 car or van drivers hospitalized after TA	816 drivers randomly selected from moving traffic (stopped for alcohol testing by police)	Positive blood/urine samples	Age, sex, blood alcohol concentration, concomitant drug exposure, season, time of day	BDZs Opioids Drug combinations	OR 5.05 (1.82, 14.04) OR 2.35 (0.87, 6.32) OR 6.1 (2.6, 14.1)	Controls are a group of drivers stopped by police at roadside. This may have introduced a bias towards null if the reason for stopping was suspicious driving behaviour

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Table I. Contd

Study (y; country)	Design (period)	Study population from which samples selected	Cases	Controls	Drug exposure ascertainment	Adjustment/stratification/ controlled/variables	Subgroups/studied drug groups	Results: risk measure (95% CI)	Comments/consideration
							Drugs + alcohol	OR 112.2 (14.1, 892)	
Dubois et al.[32] (2008; Canada)	(Jan 1993–Dec 2006)	Drivers >20 y involved in fatal TAs between 1993 and 2006	Drivers responsible for TA (as indexed by unsafe driving actions)	Drivers not responsible for TA	Blood sample analysis for BDZs, categorized according to $t_{½}$	Age, sex, other medication use, driving history	Short $t_{½}$ (<6 h): midazolam 98%	OR 1.02 (0.73, 1.42)	Drivers positive for alcohol excluded. Age stratified results: higher risk only 25–55 y
							Intermediate $t_{½}$ (6–24 h): alprazolam 80%	OR 1.53 (1.20, 1.96)	
							Long $t_{½}$ (>24 h)	OR 1.44 (1.25, 1.66)	

AL = Alabama; **ED** = Emergency Department; **GP** = general practitioner; **NSW** = New South Wales; **OR** = odds ratio; **RR** = relative risk; **SA** = South Australia; **SSRIs** = selective serotonin reuptake inhibitors; $t_{½}$ = elimination half-life; **TCAs** = tricyclic antidepressants; **VIC** = Victoria; **WA** = Western Australia.

leftover prescribed drugs or drugs obtained off-prescription during the 'unexposed period'. Nevertheless, such false exposure ascertainment shifts the results towards null findings and hence does not threaten the validity of any detected positive association between drug use and traffic accidents. Second, only a certain percentage of the outcomes (i.e. traffic accidents) are recorded in the databases. In particular, less serious accidents, which are likely to represent a significant proportion of all accidents, might have not been entered. For example, studies that recruited accident victims from hospitals[4,21,23,29,31] only include injurious traffic accidents where the injuries were serious enough to seek medical assistance. Third, data on some important confounders may have not been recorded in the registries. Many studies did adjust the analyses or matched the samples for demographic variables (e.g. age, sex) but missed some other important confounders, such as underlying illnesses for which the drugs are prescribed (e.g. depression), which can also affect driving. Inevitably, this may have left a certain degree of residual confounding. Other limitations and potential biases specific to individual epidemiological studies are noted in tables I and II.

Benzodiazepines and 'Z Drugs'

Of the three classes of drugs, benzodiazepines were the most extensively studied. Benzodiazepines have been studied in 12 case-control studies and 6 cohort studies. Of these, one case control study[26] and two cohort studies[18,38] have also examined the traffic accident risk of 'z drugs'. Based on these studies, we conducted three separate meta-analyses for case-control studies, cohort studies and accident responsibility studies.

1. *Case-control studies on benzodiazepine exposure and traffic accident risk (figure 2):* Of the 12 case control studies, 8 examined whether exposure to benzodiazepines is associated with increased odds of traffic accidents. Two studies[26,31] did not report the exposure data and numbers of traffic accidents in exposed and unexposed periods so that those two studies could not be included in the meta-analysis. However, both these studies showed a significant association between benzodiazepine exposure and traffic accidents.

Table II. Cohort studies on the roles of benzodiazepines (BDZs), antidepressants and opioids on the risk of road traffic accidents (TAs)

Study (y; country)	Design (period)	Study cohort	Ascertainment of exposure	Ascertainment of non-exposure	Outcome measure (method of reporting)	Adjustment/stratification/ controlled variables	Subgroups/different drugs	Results: risk measure (95% CI)	Comments
Ray et al.[33] (1992, USA)	With a case-crossover component for drivers involved in crashes (Jan 1984–Dec 1988)	16 262 Tennessee Medicaid enrollees aged 65–84 y, holding a driving licence	Receiving prescription for a psychoactive drug. Subgroups: current use, indeterminate use, past use	No prescriptions for BDZs	Injurious crashes reported to Tennessee Department of Safety (no. of crashes per 1000 person-years)	Age, sex, race, county of residence and calendar year Case-crossover study adjusted for alcohol use and driving frequency	*Current use of:*		
							any psychoactive	RR 1.5 (1.2, 2.9)	
							BDZs	RR 1.5 (1.1, 2.0), risk increases with dose	
							cyclic antidepressants	RR 2.2 (1.3, 3.5), risk increases with dose	
							opioid analgesics	RR 1.1 (0.5, 2.4)	
							BDZ + TCA	RR 2.1 (1.1, 4.2)	
Neutel[34,35] (1995, 1998; Canada)	(Jan 1979–Dec 1986)	323 658 individuals >20 y of age included in the Saskatchewan Health Databases	First 2–4 wk following prescription of a BDZ hypnotic (n = 78 070) or an anxiolytic (n = 147 726), but not receiving any within 6 mo preceding index prescription	Not received a prescription for a BDZ within 6 mo preceding a reference date (n = 97 862)	Traffic injury-related hospitalization following sale of indexed prescription (no. of hospitalizations)	Age, sex and other prescribed drugs	All BDZs	OR 3.1 (1.5, 6.2)	BDZ-related ORs are similar in young (<60 y) and elderly (>60 y) drivers; however, young age group is an independent risk factor for TAs
							Hypnotics (triazolam, flurazepam):		
							within 4 wk	OR 3.9 (1.9, 8.3)	
							within 2 wk	OR 6.5 (1.9, 22.4)	
							Anxiolytics (oxazepam, lorazepam, diazepam):		
							within 4 wk	OR 2.5 (1.2, 5.2)	
							within 2 wk	OR 5.6 (1.7, 18.4), risk reduces with time since prescription	

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Table II. Contd

Study (y; country)	Design (period)	Study cohort	Ascertainment of exposure	Ascertainment of non-exposure	Outcome measure (method of reporting)	Adjustment/stratification/ controlled variables	Subgroups/different drugs	Results: risk measure (95% CI)	Comments
							New users within 4 wk:		
							triazolam	OR 3.2 (1.4, 7.3)	
							oxazepam	OR 1.0 (0.3, 3.7)	
							lorazepam	OR 2.4 (1.0, 6.3)	
							diazepam	OR 3.1 (1.4, 6.5)	
							flurazepam	OR 5.1 (2.3, 11.6)	
Engeland et al.[36] (2007; Norway)	Registry-based (Apr 2004–Sep 2005)	All Norwegians aged 18–69 y (3.1 million)	Drug dispensing information. Exposed periods: first 7 days/14 days after dispensing or period corresponding to no. of dispensed DDDs	Period other than the exposed period for the given drug	TA that resulted in a personal injury (incidence rate)	Stratified for sex and age, adjusted for month of the year	*BDZs:*		
							anxiolytics (diazepam, oxazepam, alprazolam)	SIR 2.9 (2.5, 3.5)	
							hypnotics (nitrazepam, flunitrazepam, midazolam)	SIR 3.3 (2.1, 4.7)	
							natural opium alkaloids	SIR 2.0 (1.7, 2.4)	
Bramness et al.[19] (2007; Norway)	Registry-based (Apr 2004–Sep 2005)	All Norwegians aged 18–69 y (3.1 million)	Drug dispensing information. Exposed periods: first 7 days/14 days after dispensing or period corresponding to no. of dispensed DDDs	Period other than the exposed period for the given drug	TA that resulted in a personal injury (incidence rate)	Stratified according to sex and age, adjusted for month	*Diazepam:*		
							first 7 days	SIR 2.8 (2.2, 3.2)	
							first 14 days	SIR 2.5 (2.1, 3.0)	
							first 7 days in new users	SIR 3.3 (1.6, 5.8)	

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Table II. Contd

Study (y; country)	Design (period)	Study cohort	Ascertainment of exposure	Ascertainment of non-exposure	Outcome measure (method of reporting)	Adjustment/stratification/ controlled variables	Subgroups/different drugs	Results: risk measure (95% CI)	Comments
Bramness et al.[37] (2008; Norway)	Registry-based (Jan 2004–Sep 2006)	All Norwegians aged 18–69 y (3.1 million)	Drug dispensing information. Exposed period: no. of days corresponding to no. of dispensed DDD	Period other than the period defined as exposed period	TA that resulted in a personal injury (incidence rate)	Stratified according to sex and age, adjusted for month	*Sedative antidepressants (TCAs, mianserin, mirtazapine):*		
							all users	SIR 1.4 (1.2, 1.6)	
							new users	SIR 1.0 (0.7, 1.4)	
							Non-sedative antidepressants (SSRIs, MAOIs, SNRIs):		
							all users	SIR 1.6 (1.5, 1.7)	
							new users	SIR 1.6 (1.3, 1.9)	
Gustavsen et al.[18] (2008; Norway)	Registry-based (Jan 2004–Sep 2006)	All Norwegians aged 18–69 y (3.1 million)	Drug dispensing information. Exposed periods: first 7 days/14 days after dispensing	Period other than the period defined as exposed time	TA entered in Road Accident Registry (incident rate)	Month of the year, other prescribed drugs, stratified for age and sex	*Zopiclone:*		The degree of the TA (e.g. injurious, non-casualty) not specified. Risk is higher in young drivers and male drivers
							first 7 days	SIR 2.3 (2.0, 2.8)	
							first 14 days	SIR 2.0 (1.7, 2.2)	
							Zolpidem:		
							first 7 days	SIR 2.2 (1.4, 3.4)	
							first 14 days	SIR 2.1 (1.5, 2.9)	
							Nitrazepam:		
							first 7 days	SIR 2.7 (1.8, 3.9)	
							first 14 days	SIR 2.2 (1.6, 3.0)	
							Flunitrazepam:		
							first 7 days	SIR 4.0 (2.4, 6.4)	

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Table II. Contd

Study (y; country)	Design (period)	Study cohort	Ascertainment of exposure	Ascertainment of non-exposure	Outcome measure (method of reporting)	Adjustment/stratification/ controlled variables	Subgroups/different drugs	Results: risk measure (95% CI)	Comments
							first 14 days	SIR 3.1 (2.0, 4.6)	
Gibson et al.[38] (2009; UK)	Self-controlled case series (1986–Nov 2004)	Individuals aged 18–74 y met with TA and were prescribed with sedative drugs during 1986–2004. Non-driving participants excluded	Drug prescription information. Initial exposure: first 4 wk after prescription Extended exposure: reminder of the course of treatment	Period beyond the time window that spans 4 wk prior to first prescription to 24 wk after last prescription	Motor vehicle crash documented in primary healthcare database		*BDZs (all):*	IRR (99% CI):	
							first 4 wk	IRR 1.94 (1.62, 2.32)	
							extended use	IRR 2.38 (2.01, 2.81)	
							diazepam first 4 wk	IRR 1.93 (1.54, 2.43)	
							extended use	IRR 2.77 (2.20, 3.48)	
							temazepam first 4 wk	IRR 1.56 (1.12, 2.17)	
							extended use	IRR 1.36 (1.02, 1.80)	
							nitrazepam first 4 wk	IRR 1.66 (0.72, 3.86)	
							extended use	IRR 1.55 (0.89, 2.70)	
							zopiclone first 4 wk	IRR 1.03 (0.68, 1.55)	
							extended use	IRR 1.40 (1.04, 1.87)	
							zolpidem first 4 wk	IRR 1.04 (0.43, 2.48)	
							extended use	IRR 1.16 (0.60, 2.25)	
							Opioids (all):		
							first 4 wk	IRR 1.70 (1.39, 2.08)	
							extended use	IRR 1.29 (1.08, 1.54)	

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Table II. Contd

Study (y; country)	Design (period)	Study cohort	Ascertainment of exposure	Ascertainment of non-exposure	Outcome measure (method of reporting)	Adjustment/stratification/ controlled variables	Subgroups/different drugs	Results: risk measure (95% CI)	Comments
							codeine		
							first 4 wk	IRR 1.61 (1.11, 2.32)	
							extended use	IRR 1.33 (0.88, 2.00)	
							morphine		
							first 4 wk	IRR 1.16 (0.39, 3.45)	
							extended use	IRR 0.87 (0.43, 1.75)	
							dihydrocodeine		
							first 4 wk	IRR 1.60 (1.14, 2.25)	
							extended use	IRR 1.05 (0.78, 1.42)	
							tramadol		
							first 4 wk	IRR 1.46 (1.02, 2.11)	
							extended use	IRR 1.34 (1.02, 1.76)	
							SSRIs (all):		
							first 4 wk	IRR 0.92 (0.75, 1.12)	
							extended use	IRR 1.16 (1.06, 1.28)	
							TCAs (all):		
							first 4 wk	IRR 0.92 (0.73, 1.16)	
							extended use	IRR 0.94 (0.77, 1.14)	
Bachs et al.[17] (2009; Norway)	Registry-based (Jan 2004–Sep 2006)	All Norwegians aged 18–69 y (3.1 million)	Drug dispensing information. Exposed period: first 7 days after dispensing codeine or tramadol	Unexposed period: period not exposed to any CNS-impairing drugs	TA that resulted in a personal injury (incidence rate)	Adjusted for month	Codeine (all)	SIR 1.9 (1.6, 2.2)	
							Codeine (co-prescription of other impairing drugs excluded)	SIR 1.3 (1.0, 1.6)	
							Tramadol	SIR 1.5 (0.9, 2.3)	

DDDs = defined daily doses; **IRR** = incidence rate ratio; **MAOIs** = monoamine oxidase inhibitors; **OR** = odds ratio; **RR** = relative risk; **SIR** = standardized incidence ratio; **SNRIs** = serotonin-noradrenaline (norepinephrine) reuptake inhibitors; **SSRIs** = selective serotonin reuptake inhibitors; **TCAs** = tricyclic antidepressants.

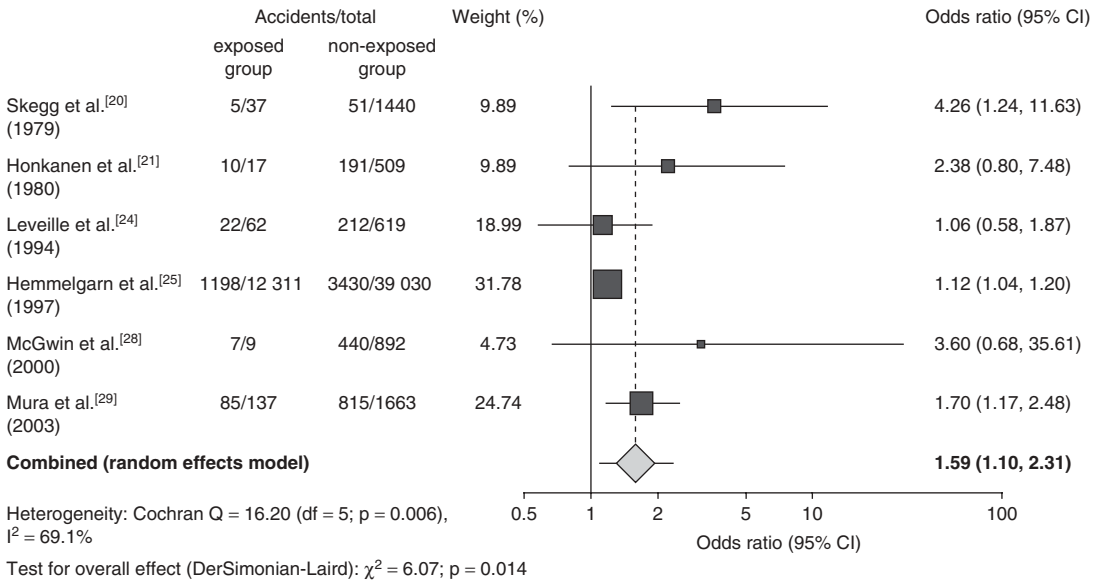

Fig. 2. Meta-analysis of case-control studies on benzodiazepines and traffic accidents. χ^2 = Chi-squared statistic for significance of the overall effect in DerSimonian-Laird random effects pooling method; **Cochran Q** = test statistic for heterogeneity of studies; **df** = degrees of freedom; I^2 = percentage of variation of study estimate due to heterogeneity (100% * [Q – df]/Q).

The first was a case-crossover study where, in a group of drivers involved in traffic accidents, the proportion exposed to benzodiazepines on the day of accident (i.e. the case period) was compared with the proportion exposed on a within-subject control period (i.e. same day of the week in up to 18 weeks prior to the accident date).[26] The adjusted odds ratio (OR) for all benzodiazepines in this study was 1.62 (95% CI 1.24, 2.12), suggesting higher accident risk associated with benzodiazepine use. The second study reported that benzodiazepine exposure was associated with a 5-fold increase in the risk (adjusted OR 5.05; 95% CI 1.82, 14.04) of injurious traffic accidents.[31]

The other six publications contained adequate data for analysis and were included in the meta-analysis (see figure 2).[20,21,24,25,28,29] The studies showed a marked statistical heterogeneity (Cochran Q = 16.20; p = 0.006; I^2 = 69.1%). Nonetheless, the overall association between benzodiazepine exposure and traffic accident risk was significant (p = 0.014), showing that benzodiazepines are associated with a 59% increase in traffic accident risk (pooled OR 1.59; 95% CI 1.10, 2.31). A previous meta-analysis by Rapoport et al.[40] in 2009 used the same set of studies; however, the authors included subject counts only for long-acting benzodiazepines in the Hemmelgarn et al.[25] 1997 study in their analysis. We included the subject counts for all benzodiazepines in the Hemmelgarn et al.[25] study because long/short half-life distinction has not been made in the other studies included in the current meta-analysis. Indeed, some other studies in the meta-analysis also included subjects predominantly exposed to short-acting benzodiazepines (e.g. the majority of subjects of the Leveille et al.[24] 1994 study were exposed to triazolam).

2. *Cohort studies on benzodiazepine exposure and traffic accident risk (figure 3):* Of the six cohort studies, two[18,19] included the same data sources used in a previous study[36] and thus those two articles were excluded. One other article was also excluded as it did not have enough information to calculate risk.[38] However, this study showed a significantly high incidence rate ratio (IRR), suggesting benzodiazepines are associated with increased traffic accident risk. The remaining three studies[33,34,36] were included in the meta-analysis (see figure 3). Similar to case-

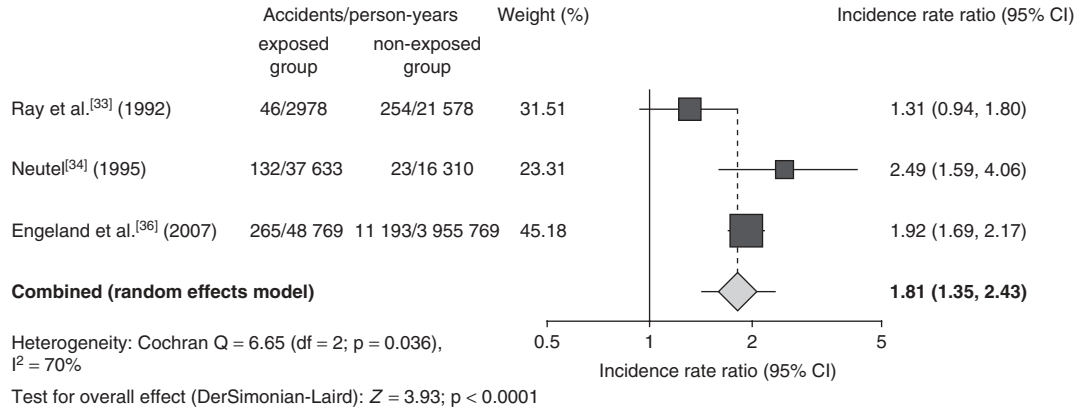

Fig. 3. Meta-analysis of cohort studies on benzodiazepines and traffic accidents. **Cochran Q** = test statistic for heterogeneity of studies; **df** = degrees of freedom; **I^2** = percentage of variation of study estimate due to heterogeneity (100% * [Q – df]/Q); ***Z*** = Z statistic for significance of the overall effect in DerSimonian-Laird random effects pooling method.

control studies, there was a significant heterogeneity among individual study results (Cochran $Q = 6.65$; $p = 0.036$; $I^2 = 70\%$). Nonetheless, the overall effect of exposure on traffic accident risk was highly significant ($p < 0.0001$), with an 81% increase of accident rates in benzodiazepine users (pooled IRR 1.81; 95% CI 1.35, 2.43).

3. *Case-control studies on benzodiazepine exposure and traffic accident responsibility (figure 4):* Six case-control studies determined whether benzodiazepines are more commonly detected in the blood of drivers responsible for accidents than in the victims (i.e. drivers who were involved but not responsible for the accident or passengers). One of the studies was excluded because of inadequate data;[26] however, this study showed a significant association between accident responsibility and benzodiazepine exposure. The other five studies were included in the meta-analysis. In the selected studies, driver responsibility was ascertained using evidence of 'unsafe driving actions' at the time of accident,[32] information

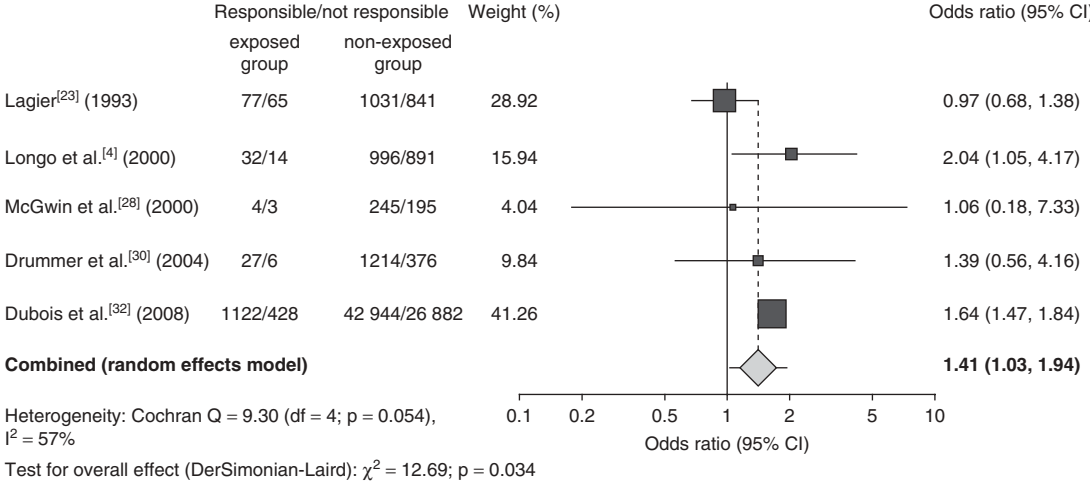

Fig. 4. Meta-analysis on accident-responsibility studies on benzodiazepines. χ^2 = Chi-squared statistic for significance of the overall effect in DerSimonian-Laird random effects pooling method; **Cochran Q** = test statistic for heterogeneity of studies; **df** = degrees of freedom; **I^2** = percentage of variation of study estimate due to heterogeneity (100% * [Q – df]/Q).

from police/researcher investigation findings[23] and comprehensive scoring systems based on drivers' attempts to mitigate an accident[4,30] as well as subjective recall.[28] The last study was the smallest and had the widest CIs.[28] There was a marginally significant heterogeneity among the studies (Cochran $Q = 9.30$; $p = 0.054$; $I^2 = 57\%$). The overall effect ($p = 0.034$) showed benzodiazepines were significantly associated with a 41% increase in accident responsibility (pooled OR 1.41; 95% CI 1.03, 1.94).

These three meta-analyses clearly confirm benzodiazepines, as a group, are associated with increased accident risk for drivers. However, different subgroup analyses in individual studies suggest several other drug and driver factors can modify this association. These confounding factors include age of drivers, therapeutic use (i.e. daytime use as anxiolytics and night-time use as hypnotics), half-life of the drug, drug dose, duration of benzodiazepine use and co-ingestion of other psychoactive substances. We conducted subgroup meta-analyses based on age and co-ingestion of alcohol but not for each of the above factors because the numbers of studies were limited.

Age

Two independent sets of evidence suggest benzodiazepine-associated traffic accident risk is lower in the elderly. First, we estimated the pooled ORs of the three case-control studies that only involved elderly (>65 years) drivers[24,25,28] and three case-control studies that comprised drivers over a wider age range starting from 18 years.[20,21,29] There was no significant statistical heterogeneity among the studies once the studies were subgrouped according to age (older group: Cochran $Q = 2.15$, $p = 0.34$, $I^2 = 6.9\%$; younger group: Cochran $Q = 3.19$, $p = 0.20$, $I^2 = 37.3\%$). The pooled OR of the older subgroup (OR 1.13; 95% CI 0.97, 1.31) was less than that of the younger subgroup (pooled OR 2.21; 95% CI 1.31, 3.73). Second, of the epidemiological studies that had participants across a wider age range, four have reported the age-stratified risk estimates for traffic accidents.[19,26,35,36] Of these, three report lower risk in older groups than in younger groups,[19,26,36] while one reported similar ORs in the young (<60 years) and the elderly (>60 years).[34] One accident responsibility study also report age-stratified risks, and found higher responsibility in young benzodiazepine users but not in their older counterparts.[32]

Therapeutic Use and Dosing Regimen

Anxiolytics are usually taken in single or multiple doses during the daytime; thus, it is possible that they increase accident risk irrespective of their short half-lives. Two cohort studies and one case-control study have categorized benzodiazepines as anxiolytics or hypnotics. All three showed increased risk with anxiolytics.[26,34,36] Two cohort studies showed an increased risk in the groups using hypnotics,[34,36] while the case-control study showed that, as a group, hypnotics did not significantly increase traffic accident risk.[26] Hypnotics are taken at bedtime, and the following day adverse effects may depend on the duration of action of the individual drugs.

Half-Life of Drugs

Two studies have examined the effect of elimination half-life of benzodiazepines, one on the risk of traffic accidents on older (>65 years) adults[25] and the other on accident responsibility.[32] The first study categorized benzodiazepines into short (≤24 hours) and long (>24 hours) elimination half-life drugs.[25] Long but not short half-life drugs were associated with increased accident risk in the elderly. The second study categorized benzodiazepines into short (<6 hours, mainly midazolam), intermediate (6–12 hours) and long (>24 hours) elimination half-life drugs.[32] New users of long and intermediate half-life benzodiazepines were at a significantly higher risk of accident responsibility, whilst those exposed to short half-life benzodiazepines showed no increased risk compared with controls.

Where individual drugs have been analysed, the accident risk is increased with the use of diazepam,[19,34,38] even after 2–4 weeks into treatment, but not with oxazepam.[34] Alprazolam was also more commonly detected in drivers responsible for an accident than in those who were not responsible.[32] Although therapeutic use of each drug was not specified in the studies, these drugs are more often prescribed as anxiolytics.

Five studies report accident risks associated with several different benzodiazepine and non-benzodiazepine hypnotics. The long-acting benzodiazepines flunitrazepam,[18] flurazepam[34] and nitrazepam[18,38] appear to increase the risk of traffic accidents. However, the medium half-life benzodiazepine hypnotics lorazepam[34] and temazepam,[38] and the short-acting benzodiazepine triazolam[34] were also found to increase the accident risk. No significant effect was observed with the very short-acting hypnotic midazolam.[32] The short-acting non-benzodiazepine hypnotic zopiclone was examined in three studies. One case-control study showed a 4-fold increase in accident risk,[26] while a large-scale cohort study reported a 2-fold increase in accident risk.[18] The other study did not show a significant change in the accident risk with zopiclone.[38] For the short-acting hypnotic zolpidem, the large-scale study reports a 2-fold increase in risk,[18] while the other study reported no significant effect.[38]

Duration of Use

Five cohort studies have examined the traffic accident risk associated with benzodiazepine use during the first 1–4 weeks following prescription and all found an increased risk of traffic accidents.[18,34,36-38] Two studies reported that the risk remained high with continuing use.[25,38]

Drug Dose

Three epidemiological studies examined the dose-response relationship between benzodiazepines and traffic accidents. They showed that higher benzodiazepine doses are associated with greater accident risk[26,33] and higher benzodiazepine concentrations in blood are associated with accident responsibility of drivers.[4] The last study reported higher accident responsibility associated with therapeutic and supratherapeutic benzodiazepine concentrations but not with subtherapeutic concentrations.

Antidepressants

Antidepressants were examined in three case-control studies and three cohort studies. One study, where all antidepressants were considered as a single group, did not show a significant increase in traffic accident risk[34] or accident responsibility.[28] There were too few studies in each category with necessary data to perform a meta-analysis.

There is no clear distinction between sedative and non-sedative antidepressants in their association with traffic accidents in patient groups investigated in epidemiological studies. In younger populations, two studies showed no significant increase in accident risk either with TCAs or selective serotonin reuptake inhibitors (SSRIs),[26,38] while one reports an increased risk with both sedative and non-sedative antidepressants.[37] However, in the elderly, the sedating antidepressants do appear to increase the traffic accident risk. Two epidemiological studies have studied antidepressants and accident risk in older drivers (>60 years). Both show that TCA use increased the risk,[24,33] with one study demonstrating that the risk increases with dose.[33] However, these studies have not examined the effects of non-sedating antidepressants and thus there is insufficient data to make any evaluation of newer antidepressants.

Opioids

The risk of traffic accidents associated with prescription use of opioids has been examined in four cohort studies and one case-control study. Of the four cohort studies, two had overlap of data sources[17,36] and one did not have adequate information to calculate risk.[38] Therefore, a meta-analysis was not performed on epidemiological studies of opioids.

Therapeutic use of opioids (as a group) was associated with a higher risk of traffic accidents in young drivers.[36,38] The effect on accidents in elderly drivers (>65 years) is inconsistent.[24,31] Limited evidence suggests that codeine,[17,38] dihydrocodeine[38] and tramadol[38] may be associated with increased accident risk at least during the first 4 weeks of use. In contrast to prescription-based studies, the detection of opioids in blood in drivers was associated neither with the accident risk[31] nor accident culpability.[30]

Drug-Alcohol Interactions and Drug Interactions

Drug-alcohol interactions are reported in three case-control studies. Benzodiazepine-alcohol combinations always showed a greater risk of traffic

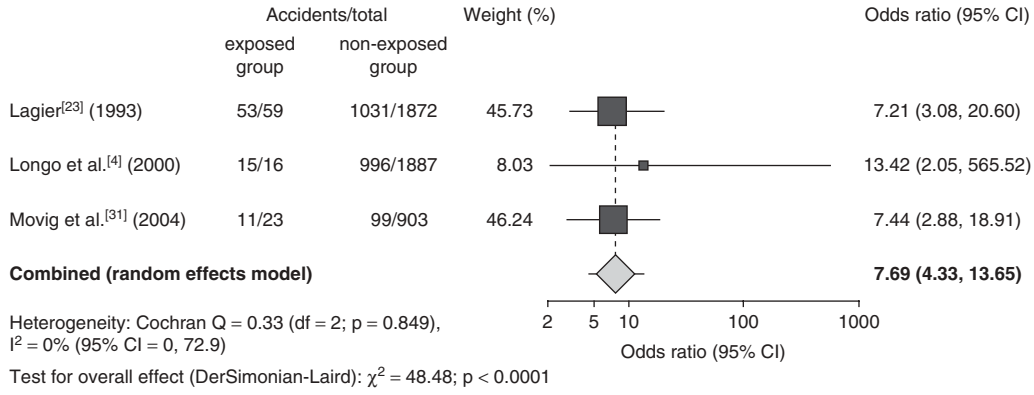

Fig. 5. Meta-analysis of case-control studies on congestion of benzodiazepines and alcohol. χ^2 = Chi-squared statistic for significance of the overall effect in DerSimonian-Laird random effects pooling method; **Cochran Q** = test statistic for heterogeneity of studies; **df** = degrees of freedom; I^2 = percentage of variation of study estimate due to heterogeneity (100% * [Q – df]/Q).

accidents[31] and accident culpability.[4,23] All three studies consisted of adult drivers over a wide age range, and determined benzodiazepine and alcohol exposure with blood/urine sample analysis. In each study, the reported OR for benzodiazepine-alcohol combination was higher than that observed with either benzodiazepines or alcohol alone (table I). The three case-control studies were combined in a random-effects model meta-analysis (figure 5). The results show that benzodiazepines can increase the odds of traffic accidents by 7.7-fold (pooled OR 7.69; 95% CI 4.33, 13.65), suggesting a marked synergistic effect of alcohol-benzodiazepine combination on risk of traffic accidents. These studies do not specify the blood alcohol levels, but all three have included some participants with blood alcohol levels below the legal limits for driving.

One case-control study and one cohort study report combined effects of psychoactive drugs on traffic accidents, both in elderly drivers. In the case-control study, use of one drug was associated with a 30% increase in the accident risk, which further increased to 100% with the use of two or more drugs.[24] Similarly, the cohort study showed a 110% increase in traffic accident risk if the driver is taking both benzodiazepines and TCAs.[33]

Experimental Studies: Effects of Benzodiazepines, Antidepressants and Opioids on Driving Performance

Appraisal of the Methodology

Any methodological concerns specific to each study are noted against the respective studies in supplementary tables 1–3 (Supplemental Digital Content). Table III summarizes the different methodological approaches of the 69 experimental studies.

Table III. Experimental study designs (both benzodiazepines and opioids were tested in one study. Some studies administered both actual and simulated driving tests)

Methodological approach		Benzodiazepines (n = 48)	Antidepressants (n = 20)	Opioids (n = 3)
Experimental design	Double-blind, placebo-controlled: crossover	41	16	1
	Double-blind, placebo-controlled: intergroup	4	2	1
	Other	3	2	1
Study samples	Healthy volunteers	35	18	2
	Patients	13	3	1
Driving test	Simulator	15	6	2
	Actual driving	34	14	1

Experimental Design

Of the 69 studies, 63 were double-blind, placebo-controlled studies, whereas six were of other designs. Of the 63 double-blind, placebo-controlled studies, 57 were within-subject crossover studies (where the same group of subjects were tested under different treatment conditions), thus ensuring maximum control over individual variations of driving performance. In many studies, attempts had been made to minimize systematic changes in performance across treatment conditions by providing adequate practice to participants and by randomizing treatment order. The participants were assigned into separate treatment or placebo groups in the other six double-blind, placebo-controlled studies (three randomized, three not specified).

Of the six experimental studies with other designs, the participants were patients in four studies.[41-44] Single groups of patients were tested before and after treatment in two of these studies, whereas a control group treated with an active drug was included in the other two. In the remaining two studies where healthy volunteers were tested, one was a randomized, double-blind study in which lorazepam served as an 'active-control' drug,[7] whilst the other one was a non-blind study.[45]

Study Samples

Participants in the majority of the studies were healthy volunteers. Although healthy volunteer studies examine the effect of a particular dose of a specific drug on driving performance, they cannot examine the interactive effects of the drugs and the conditions for which these sedative drugs are commonly prescribed (e.g. depression, insomnia, anxiety disorder, chronic pain) on driving. However, this 'confounding by indication' is accounted for in experimental studies that use patient groups experiencing insomnia,[5,46-51] anxiety,[52-54] depression[41,44] and chronic pain.[43,55]

Participants of almost all experimental studies were relatively young. Of the 69 studies, only four[56-59] had elderly participants.

Pharmacological Manipulation

Driving performance was tested after one or a few doses of drugs to examine the acute effects and/or after several days of administration to find out subacute/subchronic effects. All drugs were orally administered (except one study where fentanyl was administered transdermally) in therapeutic doses. Adequate washout periods were ensured between treatment conditions in all crossover studies.

The driving impairment observed in drug-naive individuals with fixed, single/short-term dosing regimens of experimental studies does not portray the full spectrum of impairment that can occur in real-life situations. For instance, the effects of supratherapeutic doses (that might occur with deliberate self-poisoning) on driving may be much greater, whereas patients receiving long-term medication (especially benzodiazepines and opioids) show varying degrees of tolerance so that may not exhibit the same degree of impairment observed in drug-naive subjects in experimental studies.

Driving Task and Outcome Measures

Forty-nine studies have carried out actual driving tests, while 21 have used driving manoeuvres performed in a driving simulator.

Actual car driving tests have a better ecological validity, but safety concerns in pharmacological experiments preclude testing actual driving in traffic. A standardized highway driving test developed by a research group in the Netherlands has been used in 31 experimental studies retrieved in the current review (see O'Hanlon[5] for technical details). The primary aim of the driving task is to maintain a constant lateral position and constant speed of 95 km/h. The main outcome measure, 'SDLP', indicates the degree of weaving of the vehicle from the intended path and, in turn, depends on steering control. A secondary outcome, 'standard deviation of speed (SDS)', is a measure of variability of speed and depends on accelerator control. The driver sometimes has to interact with normal traffic (e.g. overtaking a slow vehicle); however, these segments are not included in calculating SDLP and SDS. Thus, the outcome measures do not directly reflect driving ability in normal traffic. Rather, the test examines the driver's ability to operate the basic controls of

the vehicle for stable highway driving at a constant speed.

Eight other actual driving experiments focus on more complex driving manoeuvres, albeit on a closed-course. These tasks include manoeuvring around bollards (slalom task), gap estimation, reversal and parking.[6,52,60-63] Brake reaction time was an outcome measure in seven studies on actual driving.[60,64-68] One limitation of these studies is that being closed-course tests, subjects may not have had the same safety concerns as in open-road driving.

Driving simulator tests offer a safe alternative to on-road driving. Some simulator studies have measured mean variance of lateral position and mean variance of speed that are comparable with SDLP and SDS, respectively. However, there are two main limitations in predicting actual driving performance based on simulated driving. First, the artificial quality of the driver-vehicle-environment interaction compromises the ecological validity of the tests. Although participants used at least some driving controls found in a real vehicle (i.e. steering, brake) in the tests, there is a wide variation of the nature of the driving scenes and the perceptual feedback generated by the vehicle. For instance, in the simplest simulator tests, subjects had to perform a continuous tracking task (with steering) and a secondary reaction time task (using a foot pedal) in response to relatively abstract visual stimuli,[10,69-71] whereas the most complex simulator tests employed more life-like driving scenarios and emulated the forces acting upon an actual moving vehicle.[45] Second, subjects performing simulated driving tests may not consider the safety factor as much as those who undergo real driving tests, so that the driving errors in simulated driving tests may exaggerate the actual risk of driving errors in real-life driving.

Pooled estimates of SDLP for different doses of short- and long-acting benzodiazepines have been calculated in a recent meta-analysis.[40] The authors report nightly doses equivalent to ≤5 mg of diazepam significantly increase SDLP the following morning but not in the following afternoon. Doses equivalent to diazepam 10 mg or more caused a larger increase in SDLP. However, the strength of the experimental studies is the ability to assess the different doses of specific drugs on driving performance at different time intervals after dosing, whereas calculating pooled estimates across clinically heterogeneous studies may lead to loss of valuable information. In this respect, the patterns of impairment of SDLP observed with different benzodiazepine and non-benzodiazepine hypnotics[15,72,73] and antidepressants[16] have been reviewed recently by the original research group, comparing the impairment observed with drugs with what is observed with different blood alcohol levels (0.05, 0.08 and 0.1 g/dL). However, these reviews do not comprehensively review the effects of drugs on more complex driving skills, which are tested in other actual and simulated driving studies. Thus, the present review on experimental studies evaluates the effects of individual drugs on both actual and simulated driving tests.

Benzodiazepines and 'Z Drugs'

All 49 studies that we retrieved administered benzodiazepines orally in therapeutic doses. The doses were generally equivalent to diazepam 10–20 mg in most studies. Lower doses have been used in a few studies: diazepam 5–7 mg in two studies,[45,74] nitrazepam 5 mg in one study[61] and lorazepam 0.5 mg in one study.[54] Two different dosing regimens that correspond to their therapeutic use have been applied by researchers in testing anxiolytics and hypnotics. The common design for anxiolytics was to test driving performance from half an hour to about 5 hours after dosing. Hypnotics were always administered at night (replicating their therapeutic use) and driving was tested the following morning (9–10 hours after dosing) or afternoon (16–17 hours after dosing).

Benzodiazepine Anxiolytics

The results obtained in our search include five anxiolytics, *viz*. diazepam, lorazepam, alprazolam, clobazam and medazepam. The latter two drugs are not widely used at present.

Diazepam: Diazepam was tested in 11 studies. Driving performance was assessed at different times post-dose, ranging from 30 minutes[9] to 5 hours.[69] Acute increase in SDLP[74] and brake

reaction time[64] has been observed after a 10 mg dose in on-road driving tests. A single 5 mg dose did not cause a significant increase in SDLP in healthy volunteers,[74] but did increase with three-times-daily dosing.[54] The impairing effect of the latter dosing regimen was observed up to 7 days in healthy volunteers[54] and up to 3 weeks in patients with anxiety.[53] These observations suggest that even administered in low doses, repeated administration of a long-acting benzodiazepine, such as diazepam, may cause significant impairment. In driving simulator tests, 10–15 mg doses caused increased collisions,[9] increased tracking errors and reaction times,[69,71] and impairments in composite measures of overall driving performance.[56,75] In the last study, driving impairment persisted even after 1 week of treatment. One driving simulator study did not show a significant effect after diazepam 0.11 mg/kg bodyweight (approximately 7 mg) or 0.22 mg/kg bodyweight (approximately 15 mg).[45] This is the only non-blind study (healthy volunteers knew what drug they had taken) included in this review. The authors argue that those who take sedative drugs in real-life know that the drugs may affect their driving performance and thus might take extra effort to compensate. However, there was a wide intersubject variability in driving performance in this study, probably attributable to the complex driving task and relatively short practice session; these factors may also account for the lack of significant effects of diazepam. In summary, the experimental studies indicate that diazepam can impair a wide range of task processes in driving, and the impairment appears to be significant even after 3 weeks of continuing treatment. These findings are consistent with the epidemiological evidence that showed increased accident risk in diazepam users.[19,34,38]

Lorazepam: Lorazepam was tested in five studies. SDLP was the outcome measure in three experiments and all showed a significant increase with lorazepam even after 1 week of treatment.[54,76] Of these, one study was on a group of patients with anxiety; the experimenters continued treatment for 2 weeks and found a significant impairment even at the end of this period.[54] Two closed-course studies show that the drug can cause increased brake reaction time and impairment of more complex driving manoeuvres, including parking, turning and avoiding obstacles.[7,60]

Alprazolam: The two studies involving alprazolam showed a 1 mg dose can severely impair highway driving performance as indexed by SDLP.[77,78] Sustained-release preparation of the drug caused less impairment but was still significant.[78]

Clobazam: No significant short-term impairment was detected in different driving manoeuvres after 3 days of treatment with 10 mg three times daily[64] or after 20 mg in the morning.[60] One other study detected impairment after 6 days of treatment.[6]

Medazepam: The long-acting anxiolytic medazepam caused driving impairment in patients even after 3 weeks of treatment.[52]

Benzodiazepines and Newer Hypnotics

The effect of nocturnal doses of hypnotics on driving in the following morning generally depends on the half-life; however, there are some exceptions. The long half-life (>24 hours) hypnotics include flurazepam, flunitrazepam and nitrazepam.

Flurazepam (half-life of active metabolite 40–250 hours): Flurazepam was tested in six driving performance studies and all report impairment with the drug. One to two days of treatment caused a significant increase in SDLP and SDS that lasted up to 10–11 hours after 30 mg dosing in healthy volunteers, and up to 16–17 hours in patients with insomnia after 15–30 mg.[5,48] One study on patients showed the following morning's impairment was persistent even after 1 week of continuing treatment.[48] Another actual driving experiment found impaired manoeuvring skills in a slalom task 12 hours after a 15 mg dose.[63] Driving simulator tests showed increased tracking error and brake reaction time and reduced speed of driving.[10,79] These findings are consistent with the Neutel[34] 1995 study where flurazepam was associated with a 5-fold increase in the risk of injurious traffic accidents.

Flunitrazepam (half-life 18–26 hours, active metabolite 36–200 hours): A single 2 mg dose of flunitrazepam did not affect the SDLP after 10 hours in a group of young patients with sleep disturbances in one study,[49] but did cause a

significant increase that lasted 16–17 hours after two doses in another study.[5] This may be due to accumulation of this long half-life benzodiazepine. In line with these findings, another on-road driving study showed impaired steering control that persisted for more than 7 days after initiation of treatment in a group of patients with insomnia.[47] Of the three driving simulator studies, one also reported increased lateral deviation and speed variation 10 hours after a 1 mg dose.[80] These experimental findings corroborate a 3- to 4-fold increase in injurious traffic accident risk observed in a recent, large-scale epidemiological study.[18]

Nitrazepam (half-life 15–38 hours): Nitrazepam was tested in two studies. A 10 mg dose increased SDLP, which was observed 16–17 hours after a nocturnal dose in a group of young women with insomnia.[46] This impairment persisted even after 8 days of continuing treatment. This evidence supports the epidemiological findings where nitrazepam was associated with a 170% increase in traffic accidents in the first week of use.[18] A lower dose (5 mg) caused increased brake reaction time in a driving simulator 9 hours after intake, but did not cause a significant increase in the number of errors in avoidance manoeuvres in a closed-course driving test.[61]

Three other hypnotics (temazepam, loprazolam, lormetazepam) extracted in this review have intermediate plasma half-lives (8–24 hours).

Temazepam (8–22 hours): All five studies that tested the effects of temazepam used 20 mg nightly doses. SDLP was not significantly affected either in healthy elderly volunteers after a single dose[81] or in young women with insomnia who received three consecutive doses[46] the following morning (i.e. 10 hours after dosing). Two other driving studies reported that the drug did not impair manoeuverability in healthy volunteers[63] or steering control in young insomniacs[47] 10–12 hours after a single dose or multiple doses. Interestingly, temazepam also did not affect lateral position, speed deviation or reaction time in a group of elderly volunteers, even when tested only 5.5 hours after a 2:00am dose.[50] However, one cohort study shows that temazepam is associated with increased traffic accident risk during the first 4 weeks of use and, to a lesser extent, during an extended period of use.[38]

Loprazolam (half life 6–12 hours): The only study on loprazolam (1 and 2 mg) shows impairment in highway driving (as measured by SDLP) even 16–17 hours after two nightly doses in young patients with sleep disturbances.[5] This study also showed strong correlation between driving impairment and plasma drug concentration. This long-lasting impairment more closely resembles the pattern observed with long half-life hypnotics (e.g. flurazepam and flunitrazepam) rather than that observed with other intermediate half-life hypnotics (e.g. temazepam).

Lormetazepam (half-life 10–12 hours): Effects of lormetazepam on driving was tested in five experimental studies. Lormetazepam 1 or 2 mg administered at night did not have significant acute or subchronic effects in the morning on SDLP in patients with insomnia.[48] Healthy volunteers showed a significant impairment 10 hours after the first 2 days of administration but not 16 hours after the second dose.[70] In driving simulation experiments, lorazepam 2 mg increased tracking errors and reaction time when tested at 1–5 hours,[69] but did not have significant acute[10,70,82] or subchronic[10] effects when tested the morning following a nightly dose.

Short-acting hypnotics that have been tested for the effects on driving include triazolam, midazolam, zopiclone, zolpidem, zaleplon and eszopiclone.

Triazolam (half-life 2–3 hours): One driving simulator study showed increased tracking errors up to 4.5 hours and delayed brake reaction time up to 1.5 hours after triazolam 0.25 mg,[71] but no significant effects were observed on simulated driving when tested the morning following a 0.25 mg or 0.5 mg nightly dose.[61,79] However, given that there is some evidence that triazolam may be associated with increased accident risk,[34] it is worth investigating drug effects also with on-road driving tests.

Midazolam (half-life approximately 2 hours): The only study on midazolam did not show a significant impairment in brake reaction time 10 hours after midazolam 15 mg.[65]

Zopiclone (half-life 5–6 hours): Effects of zopiclone have been tested in four standardized

on-road driving studies and five driving simulator experiments. All studies used the standard treatment dose of 7.5 mg. Despite the short half-life of the drug, there is consistent evidence that SDLP increases 5 hours[83] and 10 hours after a bedtime dose in healthy young volunteers,[81,83,84] and 10 hours post-dose in elderly individuals.[58] One driving simulator study also reported increased lateral position deviation 10 hours after dosing but not after 12 hours.[80] Other driving simulator studies reported increased collisions after 9–11 hours,[51] increased tracking errors after 1.5 hours,[71,85] and delayed brake reaction time after 1.5 and 4.5 hours.[71] These findings parallel the markedly high traffic accident risk associated with zopiclone in epidemiological studies.[18,26] This is an unexpected trend given the short plasma half-life of zopiclone.

Zolpidem (half-life approximately 2 hours): Two actual driving studies and one simulator study examined the effects of zolpidem 10 mg around 4–5.5 hours after middle-of-the-night dosing. This dose increased SDLP and SDS in healthy volunteers in both actual driving studies,[81,86] and increased the variance of lateral position in patients with insomnia in the simulator study.[50] Similarly, increased poor lateral position and speed control were reported at 2 hours but not 13 hours after a 10 mg dose in another driving simulator study.[87] One actual driving study and two simulator studies showed that zolpidem 10 mg does not impair SDLP in young insomniacs,[49] or mean lateral position variance in healthy elderly[80] or young insomnia patients,[51] when tested the following morning (i.e. 9–10 hours post-dose). The experimental evidence indicates that a 10 mg bedtime dose of zolpidem does not affect the basic control processes of driving the following morning but does impair if taken in the middle of the night. The largest cohort study conducted so far reports a 2-fold increase in traffic accident risk in young zolpidem users during the first 4 weeks of use,[18] while another did not find a significant increase in the risk.[38] However, the exposure was based on prescription records, so that neither of the two studies is able to provide information on actual time of administration of the hypnotic. There is also a theoretical possibility that even if the basic control processes of driving are intact the morning following a bedtime dose (as has been observed in the experimental studies), more complex driving skills required for accident avoidance may still be impaired.

Zaleplon (half-life 1 hour): Effects of zaleplon have been examined in only three on-road driving studies. They showed that SDLP or SDS in healthy young individuals are not affected by a 10 or 20 mg dose when tested 10 hours (i.e. the morning after a bedtime dose)[84,86] or 4–5 hours after dose administration[83,86] (i.e. the middle of the night dose).

Eszopiclone (half-life 6 hours): According to the two driving experiments conducted so far, eszopiclone 3 mg did not affect the brake reaction time in either healthy young or elderly individuals, when tested 9–19.5 hours post-dose.[68]

Antidepressants

Antidepressants have been used in therapeutic doses in almost all studies. Driving performance has been tested 1–5 hours after dosing, except in five studies[44,88-91] where drugs were administered at night and driving was tested the following morning.

The effect of antidepressants on automobile driving seems to be determined mainly by the sedative effect profile, and probably also by the anticholinergic effects of the drugs.

Sedating Antidepressants

Amitriptyline: Effects of amitriptyline have been examined in four actual driving experiments and four simulated driving tests. Three showed acute increase in SDLP after 25 mg[5,90] and 75 mg.[92] A comparable driving simulator experiment found increased SDLP and headway variability 4 hours after amitriptyline 25 mg,[93] with a moderate positive correlation between plasma amitriptyline concentration and SDLP.[8] Only one study tested driving the morning following a nocturnal dose.[90] The investigators found increased SDLP even 13 hours after a 25 mg nocturnal dose in patients with neuropathic pain. The other four studies reported impaired tracking/steering control[71,94,95] and brake reaction time[71,96] 2–5 hours after a 50 mg dose.

Other tricyclic and related antidepressants: All studies where healthy adult volunteers were administered sedative antidepressants in multiple daily doses reported increased SDLP. Acute (1–4 hours post-dose) impairment of SDLP has been reported with imipramine 50 mg twice daily,[57] doxepin 25 mg three times daily,[5,97] and mianserin 10 mg three times daily.[5,97,98] Three studies on the effects of nocturnal doses showed that SDLP was increased the following day (13–17 hours post-dose) with mirtazepine 15 mg[91] and 30 mg,[89] but not after dothiepin 75 mg[88] or mianserin 30 mg.[91] The only experimental study on elderly participants showed no acute effects (2 hours post-dose) of imipramine 50 mg on SDLP, although a significant increase was observed in their younger counterparts.[57]

Effects of continuing treatment: Post-dose impairment in SDLP remained significant even after 1–2 weeks of treatment with mianserin,[97,98] but not with imipramine,[57] doxepin,[97] mirtazepine[89] or amitriptyline.[90,92] Only three studies examined the subchronic effects of sedative antidepressants on driving in patient groups. One study of chronic pain patients showed that the impairing effects (as indexed by increased SDLP) of amitriptyline disappear after 15 days of continuing treatment.[55] The other two driving simulator studies on depressed patients showed improvement of performance after 2–4 weeks of treatment with mirtazepine.[41,44] The latter study also found that performance did not improve in an untreated control group.[44]

Non-Sedating Antidepressants

In contrast to tricyclic and other sedating antidepressants, newer non-sedating antidepressants do not appear to have acute or subacute effects on driving when tested with standardized highway driving tests or driving simulation tests. Absence of any significant acute or subchronic effects on SDLP or speed variability in healthy volunteers has been demonstrated with the SSRIs paroxetine (10 mg),[93] fluoxetine (20 mg)[88] and escitalopram (10–20 mg),[89] the serotonin-noradrenaline (norepinephrine) reuptake inhibitor venlafaxine (37.5–75 mg twice daily)[98] and the monoamine oxidase inhibitor moclobemide (200 mg twice daily).[97] The only study on depressed patients reports that driving performance (as tested on a simulator) improves after 2 weeks of treatment with the non-sedating antidepressant reboxetine, as well as with the sedative antidepressant mianserin.[41]

Opioids

Only three experimental studies examined the effects of opioids on driving (supplementary table 3, Supplemental Digital Content). One study on healthy volunteers showed increased collisions in a driving simulator task after a single 50 mg dose of codeine,[9] while the other showed no significant acute effects of an oxycodone-paracetamol combined preparation (5 mg/325 mg and 10 mg/650 mg) on SDLP or SDS.[99] However, in the latter study, a dose-response relationship was observed and subjective reporting indicated that the participants had to apply more effort in driving compared with control conditions. The only study on patients with chronic pain was a pre-test, post-test design where driving performance was tested before and 2 months after initiation of a transdermal fentanyl treatment.[43] There was no significant change in performance as assessed with a driving simulator test.

Drug-Alcohol Interactions and Drug-Drug Interactions

A limited number of experimental studies compared the effects of drugs alone with drug-alcohol combinations on driving skills. The addition of alcohol was found to worsen the acute impairment caused by lormetazepam,[69] flurazepam,[79] triazolam[71] and amitriptyline.[95]

One study reports the interactive effects of diazepam with amitriptyline and with mirtazepine. Severity of tracking error was greater with diazepam-antidepressant combinations than with any of the drugs alone.[71]

Discussion

The present paper reviews the research evidence on the effects of three different classes of sedative drugs (benzodiazepines, antidepressants and opioids) on driving performance, and their association with traffic accidents, taking into ac-

count different drug and patient factors that modify these effects in a practical context.

Our meta-analyses of case-control and cohort studies indicate that benzodiazepines, as a group, are associated with a 60–80% increase in the risk of traffic accidents. Meta-analysis of case-control studies on accident culpability shows that drivers responsible for traffic accidents are 40% more likely to be positive for benzodiazepines than those who are not responsible, suggesting that benzodiazepines actually may play a causative role in traffic accidents.

Deleterious effects of benzodiazepines are potentiated by co-ingestion of other sedative substances. The present review shows that the presence of alcohol and benzodiazepines was associated with a 7.7-fold increase in the risk of a traffic accident. Evidence from experimental studies supports this assertion. Benzodiazepines also interact with sedative antidepressants to impair driving skills and increase the risk of accidents. Although drug warning labels and consumer sites generally warn about the increased sedative effects of drug-alcohol combinations, they do not specify the effects on driving. We believe that drug information sheets/warning labels should specify this interactive effect on driving, and prescribers should warn patients that the benzodiazepine-alcohol combination may markedly increase the risk of accidents even if the blood alcohol levels are below the legal limit (generally 0.5–0.8 g/dL in most countries).

Epidemiological studies also suggest that benzodiazepine-associated traffic accident risk is less in elderly drivers than in younger adults. Low benzodiazepine-associated accident risk in elderly drivers may occur for a variety reasons. Elderly individuals tend to be prescribed lower doses of benzodiazepines compared with their younger counterparts. Perhaps elderly drivers taking benzodiazepines may appreciate the potential deleterious effects of drugs more and resort to safer driving patterns or limit driving while they are taking drugs. Epidemiological studies, however, do not provide information of drug doses or driving patterns and thus fail to support or refute any of the above speculations. Only a few driving experiments have been carried out in the elderly;[56,58,59] they do not make a clear distinction between drug effects on the young and the elderly. Although driving experiments in elderly drivers who have been given sedative drugs may have safety and ethical concerns, further research in this group is necessary because increased life expectancy and independence has increased the proportion of elderly drivers in the community, and many elderly patients take benzodiazepine hypnotics.

General patterns emerging from epidemiological and experimental studies also indicate that anxiolytics, taken in single or multiple doses during the daytime, tend to impair driving somewhat independently of their half-lives. As for hypnotics, the accident risk and the possibility of daytime driving impairment tend to be related to their plasma half-lives, but with exceptions.

Results of the experimental studies suggest that diazepam, flurazepam, flunitrazepam, nitrazepam and the short half-life non-benzodiazepine hypnotic zopiclone may cause significant driving impairment, and the findings of epidemiological studies show that use of these same drugs are associated with a significant increase in traffic accident risk. The accident risk remains elevated, at least during the first 2–4 weeks after commencement of treatment, and nocturnal doses cause impaired driving performance, at least leading up until the following afternoon in the case of benzodiazepine hypnotics and the following morning in the case of zopiclone. Diazepam is the most extensively studied benzodiazepine. Even though widely prescribed, there is strong evidence that diazepam worsens driving performance and is associated with increased accident risk, at least for the first 3–4 weeks after commencement of anxiolytic treatment. Impairing effects of the above sedative drugs raise important, but controversial legal implications. The 2- to 3-fold increase in accident risk associated with these long-acting benzodiazepines and zopiclone is equivalent to what has been observed with a blood alcohol concentration of 0.05–0.08 g/dL,[100,101] which is above the legal limits for driving in most countries. A series of on-road driving studies also illustrate that SDLP observed with therapeutic doses of the hypnotics is above these legal limits for alcohol.[14] For hypnotic medication, an option for prescribers

is to avoid these hypnotics (flurazepam, flunitrazepam, nitrazepam and zopiclone) if patients are engaged in driving. Relatively safer alternatives would be shorter acting hypnotics, such as triazolam, temazepam, zolpidem and zaleplon, which were not found to cause driving impairment, at least in experimental studies (although there is evidence that some of the drugs are associated with increased accident risk). Still, patients should be cautioned against the possible effects on driving and the course of hypnotic treatment should be continued only for the minimum required period. We believe, in the present clinical context, patients with anxiety who are prescribed diazepam should be strongly encouraged not to drive, at least during the first 4 weeks of treatment. However, unlike hypnotics, the research evidence does not readily offer safer alternatives for prescribers; all other anxiolytics, with daytime dosing, were found to impair driving, at least in healthy volunteers. Large-scale epidemiological studies and experimental studies on patient groups are imperative to examine the safety of other anxiolytics.

There is no clear distinction between sedative and non-sedative antidepressants in their association with traffic accidents in epidemiological studies, particularly in young patients using antidepressants.[26,37,38] Presumably, one major source of confounding in patient studies is the condition to which the drugs are prescribed (i.e. depression). Antidepressants interact differently with depression at different stages of treatment to influence driving ability. To begin with, cognitive and psychomotor deficits of depression itself may limit driving capacity of an individual. Because the antidepressants do not bring therapeutic effects immediately after commencement of treatment, depressed patients may show driving impairment during the first 1–2 weeks of treatment, even if their antidepressants are non-sedative. Patients taking sedative antidepressants may be affected more than those on non-sedating antidepressants during this initial stage because of the acute sedative effects of the drugs, as has been observed in healthy volunteers in experimental studies. Continuing treatment beyond 3–4 weeks tends to improve depression, and patients tend to become tolerant to sedative effects, depression begins to be alleviated and patients may develop tolerance to sedative effects of sedating antidepressants. This is supported by limited experimental evidence that showed that young patient groups treated with sedative or non-sedative antidepressants improved their driving skills after a few weeks[41,44,90] while untreated patients did not.[44] In general, epidemiological studies have failed to eliminate residual confounding effects of depression because they have basically compared those who use antidepressants (i.e. depressed patients) with those who did not (most likely non-depressed individuals). Case-crossover[26] and self-controlled case-series[38] studies have attempted to overcome this methodological constraint by employing within subject designs, thus controlling for depression, at least to some extent.

Limited evidence suggests that TCAs may be associated with an increased traffic accident risk in the elderly. Experimental evidence is very scarce on this group and hence it is impossible to confirm whether this is due to differential effects of antidepressants, depression or a complex interaction between the two.

Few epidemiological studies conducted so far suggest that opioid users (at least in young drivers) may be at greater risk of traffic accidents in the first few weeks of treatment; however, scarce experimental data do not provide conclusive evidence on whether opioids impair driving in patients receiving treatment. As with antidepressants, the interactive effect of opioids, and underlying conditions such as chronic pain, on driving performance is also not clear.

Apart from the biases and limitations of the individual studies, there are certain limitations of the present review. We could not include certain epidemiological studies[26,31,38] in the meta-analyses as they did not contain the necessary information required to calculate risk estimates that are compatible with the majority of the studies. Although the magnitudes of the risk estimates of these studies were different from the pooled estimates, the direction of the association was the same. It has to be acknowledged that even the best efforts of combining epidemiological and experimental evidence failed to establish a complete causative pathway between psychoactive drugs and traffic accidents. In other words, epi-

demiological studies showed that some of these drugs are associated with (but not necessarily cause) an increased risk of traffic accidents. Driving performance studies showed that those drugs *caused* an impairment of *driving*, but this does not necessarily mean that the impairment is practically significant enough to increase the risk of accidents. As a compromise, some researchers have calibrated driving performance measures (e.g. degree of weaving of vehicle as indexed by SDLP) against different levels of exposure to substances already known to increase accident risk (e.g. different blood levels of alcohol).[5] Future research can further narrow this gap in the path of causation by correlating the performance measures (e.g. SDLP) directly with the risk of accidents of the same subjects (e.g. number of traffic accidents the test subjects encounter during a certain fixed time period before and after SDLP measurement). In fact, a similar approach had been used recently to validate trail-making test B performance (which is a neuropsychological measure of visual scanning, visuomotor coordination, divided attention and executive functions) as a predictor of motor vehicle crash risk.[102]

Conclusions

Although there are inherent limitations in pharmacoepidemiological and experimental study designs in detecting the effects of sedative drugs on driving and traffic safety, a clearer picture emerges in combining the findings of the two different types of studies. The results show that benzodiazepine use is associated with a significant increase in the risk of traffic accidents and accident responsibility of drivers. The accident risk is markedly increased by co-ingestion of alcohol. Driving impairment was generally related to plasma half-lives of hypnotics, but with notable exceptions. Anxiolytics, with daytime dosing, impaired driving independent of their half-lives. We believe that these findings will help in formulating more specific clinical guidelines and precautions in the use of benzodiazepines.

Limited epidemiological evidence suggests that TCAs may be associated with increased accident risk, at least in the elderly. Experimental studies also indicate that sedative, but not non-sedative antidepressants impair driving performance at the initiation of treatment. However, long-term experimental studies with regular follow-up are necessary to elucidate how antidepressants and their complex interaction with depression affect driving performance over the course of treatment in depressed patients. Opioid users may be at a higher risk of traffic accidents; however, experimental evidence on their effects on driving is scarce.

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