The impact of medicinal drugs on traffic safety: a systematic review of epidemiological studies.

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THE IMPACT OF MEDICINAL DRUGS ON TRAFFIC SAFETY: A SYSTEMATIC REVIEW OF EPIDEMIOLOGICAL STUDIES

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Key points:

- Taking benzodiazepines has been identified as a risk for road traffic crashes in several epidemiological studies. However, data are missing for other medicinal drugs.
- Main methodological issues are confounding by indication and grouping of drugs with different properties.
- Exposure assessment methods are heterogeneous, partly explaining the inconsistent literature results.

ABSTRACT

Purpose: To evaluate the quality of epidemiological research into effects of medicinal drugs on traffic safety and the current knowledge in this area.

Data sources: The bibliographic search was done in Medline electronic database using the keywords: ((accident* or crash*) and traffic and drug*) leading to 1141 references. Additional references were retrieved from the Safetylit website and the reference lists of selected studies. Original articles published in English or French, between April 1st, 1979 and July 31st, 2008, were considered for inclusion. We excluded descriptive studies, studies limited to alcohol or illicit drug involvement, and investigations of injuries other than from traffic crashes. Studies based on laboratory tests, driving simulators or on-the-road driving tests were also excluded. Eligible studies had to evaluate the causal relationship between the use of medicinal drugs and the risk of traffic crashes. Study quality was assessed by two independent experts, according to a grid adapted from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Results: 22 studies of variable methodological quality were included. Definition of drug exposure varied across studies and depended on the data sources. Potential confounding due to the interaction between the effects of the medicinal drug and disease-related symptoms was often not controlled. The risk of motor-vehicle crashes related to benzodiazepines has been amply studied and demonstrated. Results for other medicinal drugs remain controversial.

Conclusion: There is a need for large studies, investigating the role of individual substances in the risk of road traffic crashes.

INTRODUCTION

Traffic crashes are a common cause of death in many countries. Among the numerous risk factors (eg, speed, alcohol, talking on cell phones, road infrastructures), the effect of medicinal drugs has not received sufficient attention. Assessment of effects of medicinal drugs on driving ability by laboratory tests, driving simulators or on-the-road driving tests provides helpful insights on potential impact, but only partially assesses the impact in "real life" conditions where driver behaviour, health status, and road traffic environment interact. Reports on the state of knowledge about drugs and driving were published in 1999 [1] and 2003 [2], showing an increase concern about the role medicinal drug use may play in road traffic crashes. In 2003, a European Safety Action program was set up to encourage research on the effects of medicinal drugs, in order to establish a European classification regarding road safety [3]. Two literature reviews, focusing on a few medicinal drugs (benzodiazepines, opioids, antihistamines and antidepressants), concluded that benzodiazepines represent a major traffic safety problem but remained cautious about other medicinal drugs [4 5]. The aim of this article is to review available epidemiological studies, their results and methodological issues, in order to make recommendations for further research.

METHODS

Search strategy

The bibliographic search was done in Medline electronic database using the keywords: ((accident* or crash*) and traffic and drug*). We updated the search using the Safetylit website which provides an updated literature on injury prevention with a special section on "alcohol and other drugs". The reference lists of papers considered for inclusion were scanned for any further potentially eligible studies. Original articles published in English or French, between April 1st 1979 (oldest article we included) and July 31st, 2008 (end of inclusion

period), were considered for inclusion. We excluded descriptive studies, studies limited to involvement of alcohol or illicit drugs, and studies of injury risk other than in traffic crashes. Studies based on laboratory tests, driving simulators or on-the-road driving tests were also excluded. Eligible studies were those that evaluated the causal relationship between the use of medicinal drugs and the risk of traffic crashes.

Quality assessment

A reading grid was adapted from the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology) [6] and from the quality assessment checklists published by Salmi [7] (see Appendix 1). Criteria covered methods of selecting participants, data collection regarding outcomes, exposures and potential confounders, statistical methods and reported results, as well as discussion content.

Participant selection was evaluated according to the relevance of eligibility and exclusion criteria to reflect a general population of drivers, the choice of sources, the independence of selection from the event or the drug exposure, and the comparability of the reference group. We considered the way medicinal drug exposure was assessed. In studies on medicinal drug consumption and crash risk, several potential confounders should be measured and controlled in analyses. Apart from subjects' age and gender, interaction between disease-related symptoms and the effects of the medicinal drug used to treat the disease, which can both modulate the risk of crash, should be addressed. Other important variables to be measured are the number of kilometres driven in each group and the consumption of alcohol or other drugs. We assessed the relevance of statistical methods and results presentation and discussion. Two authors (EL and LO) reviewed the selected studies independently according to the grid criteria. Disagreements were referred to a third reviewer (LRS) and resolved by discussion.

RESULTS

Bibliographic search retrieved 1141 references from which 16 eligible studies were selected on the basis of their title and abstract. An additional six studies were found either from a Safetylit website search or from the reference lists of the initial 16 studies. This process led us to select 22 epidemiological studies of the impact of medicinal drugs on the risk of traffic crashes [8-29]. Their methodology and main results are presented in Table 1.

Quality of available research

Two sources for the outcome variable (the crash) are described in these studies. In eight studies, case selection was based on emergency admission to hospital for injuries related to the crash [16 18 20 21 23 26-28]. Accident record databases represented the most frequent source for identification of subjects involved in traffic crashes [8-15 17 19 22 25 29]. Drummer *et al* [11] focused on fatal crashes while two other studies only considered non-fatally injured drivers [18 27].

Case-control was the most frequent design [10 13 15-17 20 23-25 27]. Two strategies were used to select an appropriate control group, composed of drivers who have not been involved in a crash. The first method consisted of random selection from moving traffic or at petrol stations [16 20]. Selection was therefore done on a voluntary basis, which can lead to a selection bias. In the second method, control subjects were selected from the source of case data, such as health insurance records [17], driver licence records [10 13 15 19 25], general practitioner records [23] or hospital admissions [27]. Depending on the characteristics of the source population, extrapolation to the general driver population must be done with caution, especially if there is no indication that these controls actually drive.

Among selected epidemiological studies, five were responsibility studies [11 18 19 24 26] which can be viewed as a particular case-control study. The main principle is that if a medicinal drug contributes to crash causation, it would be over-represented in drivers whose responsibility in

the crash was demonstrated compared to non-responsible drivers. Responsibility analysis, based on police records, must be objective and independent of data related to medicinal drug consumption. A standardized method to determine the level of driver responsibility was described by Robertson and Drummer [30] and applied in studies by Drummer *et al* [11] and Longo *et al* [18]. The responsibility determination criteria were not described precisely in the other three studies [19 24 26].

Barbone *et al* [8] and Ray *et al* [22] used a case-crossover design, where the exposure risk to a given medicinal drug in a period immediately before the crash was compared with the exposure risk in an earlier period. Each subject was his own control and confounding due to all fixed characteristics was therefore eliminated, including genetics, personality, education, lifestyle and chronic diseases. This design, appropriate to study the effects of episodic exposure on the risk of acute events [31], is not adapted to chronic exposure.

Exposed/non-exposed studies have also been conducted, in which users and non-users are followed up for subsequent road traffic crashes [9 12 14 21 22 28 29]. Unlike case-crossover designs, these studies ensure independence of subject selection from outcome and can address chronic consumption. This is not always true in case-control studies.

Available data about medicinal drug prescription (eg, dose, treatment duration) depended on national records. The link between prescription and actual consumption is estimated in various ways. Exposure periods can be estimated according to the date of dispensation and the number of defined daily doses (DDDs) dispensed [9 12 25 29] or according to the prescribed duration of treatment when known [8 15]. Sensitivity to definition of consumption period has been tested, comparing the results obtained for a presumed exposure of seven days with fourteen days, starting the day after dispensing [9 12 14]. Incident use was defined as exposure after a non-use period to assess the effect of treatment initiation [9 14 15 21 25 28 29], as opposed to chronic consumption defined by repeated exposure [10 13 28].

Drug exposure assessment was performed by the analysis of urine or blood samples in six studies [11 16 18 20 24 27]. This method measures actual use and offers the advantage of accounting for non-prescribed medicinal drugs. The main limits are the small number of substances tested and the time period between crash and sampling which may be critical for some medicinal drugs.

McGwin *et al* [19] collected medicinal drug exposure data during a telephone interview, leading to possible bias due to self-reporting. Indeed, Honkanen *et al* [16] showed that only half of the patients in whom benzodiazepines were detected by serum analysis reported having taken these medicinal drugs.

Another issue relates to the grouping of drugs according to therapeutic class, often for reasons of statistical power. As an example, all benzodiazepines were assessed as a single class of exposure [8 11 17-20 22 27], whereas, in this class, drugs can have different pharmacokinetic properties: benzodiazepines with longer half-lives are probably more likely to be associated with an associated risk of road traffic crash [15].

Concomitant consumption of non-medicinal psychoactive substances was sometimes controlled in the analysis: illicit drugs in two studies [11 18], alcohol in five studies [11 18 20 21 24]. The frequency of driving was measured and accounted for in statistical models in only two studies [17 19]. A few studies considered the potential interaction with medical conditions [10 13 15 17 19 25]. McGwin *et al* [19] estimated the risk for angiotensin-converting enzyme inhibitors and anticoagulants adjusted for the conditions for which they are prescribed, and the same strategy was used for nonsteroidal anti-inflammatory drugs and arthritis. In the study of the effect of warfarin, adjustment was made for cardiovascular events and strokes [10]. Other studies adjusted for a summary chronic disease score based on selected prescription medications used in the management of chronic conditions [13 15 17 25].

The effects of medicinal drugs on road safety

Benzodiazepines

The impact of benzodiazepines on the risk of car crashes has been extensively considered in several studies [8 11 12 14-24 26-28]. The strength of the associations and the consistency between studies indicate that benzodiazepines are a cause of car crash risk, although part of the effect could result from the indication of benzodiazepines (sleep problems). The effects of benzodiazepines on the risk of crash have been demonstrated in the elderly [15 22], but also among younger drivers [8 14 21 28]. The effects of treatment initiation have been explored [14 15 21 28]. A cohort study about the risk of hospitalisation for traffic crash injuries showed a diminished risk with elapsed time from the new prescription fill-date [21], probably reflecting tolerance to medicinal drug effects or decreasing doses or use over time. In the case-crossover study, a dose-response relationship between benzodiazepine consumption and crash risk was described [8]. Benzodiazepine hypnotics and anxiolytics have been studied separately [8 12 21], as well as long and short half-life benzodiazepines [15] and individual drugs (eg, zopiclone, zolpidem, diazepam, lorazepam) [14 28]. Four studies did not find any significant relationship. Two of them lacked sufficient statistical power [11 17], and in the third information was obtained via self-report [19]. In the last study, the authors note that the assay used to detect blood benzodiazepines measures certain benzodiazepines poorly, especially triazolam [24].

Antidepressants

Two studies conducted in older drivers found a significant association between the risk of being involved in a car crash and the consumption of tricyclic antidepressants (relative risk=2.2 [1.3-3.5] [22] and odds ratio=2.3 [1.1-4.8] [17]). Bramness *et al* found an increased risk for drivers who had received a prescription for any antidepressant, slightly higher for young drivers (18-34 years old), but without adjusting for the use of other narcotics and without

being able to distinguish between the effects of the medicinal drugs and depression [29]. Two other studies showed no association, probably because of insufficient statistical power [19 20]. However, despite a study population of 410 306 people aged at least 18 years, Barbone *et al* [8] found no relationship with the risk of traffic crash, for selective serotonin-receptor inhibitors or for tricyclic antidepressants, suggesting the risk to be specific to older drivers.

Lithium

In a nested case-control study, the risk of being involved in an injurious motor vehicle crash for elderly people who use lithium was found to be increased two-fold. Carbamazepine, another common mood stabiliser, also used in epilepsy, was not associated with the risk of traffic crashes [13].

Opioids

Engeland *et al* [12] found that the risk of road traffic crashes was increased in users of natural opium alkaloids such as codeine, morphine and oxycodone (SIR=2 [1.7-2.4]), and that the risk was higher in the 18-54 age group. In the case-control study by Leveille *et al* [17], opioid analgesic use was also associated with an elevated crash risk in older drivers (OR=1.8 [1-3.4]). Mura *et al* [27] also found the association significant, but no distinction was made between licit and illicit use of opiates as only biological samples were used for their detection. No significant association was found by three studies which may have lacked statistical power [11 20 23], and by Ray *et al* [22]. A longitudinal study from a cohort of 13 548 French workers suggested that pain and pain treatment could be associated with the risk of crash. The authors noted, however, that severe pain is more likely to be treated and may itself be associated with poorer driving performance [32].

H1 antihistamines

A few studies explored the association between H1 antihistamines and car crashes. Skegg *et al* identified only 3 antihistamine users (5.3%) among a small sample of 57 cases [23]. In the studies by Leveille *et al* [17] and by Ray *et al* [22], both conducted in the elderly, the association was not significant. Nevertheless, Howard *et al* [33] showed that histaminergic consumption was associated with the risk of traffic crashes in professional drivers**.** There is a lack of epidemiological data on impact of the different generations of antihistamines which have different ability to cross the blood-brain barrier and induce sedation.

Diabetic treatment

The risk of crashes for diabetic drivers is linked to degenerative complications and to hypoglycaemic seizures related to treatment. Inconsistent results have been published about the role of diabetes and its treatment in causing traffic crashes, probably because of the heterogeneity in treatment regimes [34-37]. A responsibility study conducted in the elderly did not find any association between diabetes and at-fault crash involvement and no interaction with treatment type [19 36]. Traffic injury risk has been reported to be 2.6-fold higher in older diabetic drivers, especially those treated with insulin (OR=5.8 [1.2-28.7]) but not in those using oral hypoglycaemic agents [35]. Hemmelgarn *et al* [25] found the rate ratios for current users of insulin monotherapy were 1.4 [1.0-2.0] and 1.3 [1.0-1.7] for sulfonylurea and metformin combined. The authors note the difficulty of distinguishing between medicinal drug effects and diabetes-related complications since treatment is strongly correlated with disease progression.

Cardiovascular drugs

Among the medicinal drugs considered in epidemiological studies, calcium channel blockers were not associated with an increased risk of crashes [12], and were associated with a reduced risk of at-fault crash involvement, as well as vasodilators [19]. In the latter study, anticoagulants and angiotensin-converting enzyme inhibitors were positively associated with being at-fault for a crash but the odds ratios were no longer significant after adjustment for concomitant diseases [19]. In a recent case-control study, the use of warfarin, an anticoagulant, was not associated with an elevated rate of injurious motor vehicle crash [10].

Carbamates

Carisoprodol, a muscle relaxing drug, has been considered in a pharmacoepidemiological study because of its central nervous system depressant potential. The standardised incidence ratio for being involved in a crash having been prescribed carisoprodol was 3.7 [2.9-4.8] [9].

Nonsteroidal anti-inflammatory drugs

Recently, Engeland *et al* [12] raised the question of nonsteroidal anti-inflammatory drug (NSAID) effects in the central nervous system, as they found a significant association with the risk of traffic crash (OR=1.5 [1.3-1.9]). This result could be an indicator of clinical disability in some arthritic conditions. McGwin *et al* found that NSAID association with an increased risk of at-fault involvement in crashes persisted after adjustment for arthritis which was also independently associated with crash risk in females. The authors note however that some NSAID users may be undiagnosed for musculoskeletal impairments [19].

Discussion

The 22 studies included in this systematic review were of variable methodological quality. Several different research methods were used, leading to difficulties to compare them. The

sample populations were different, ranging from victims of road traffic crashes with personal injury, victims hospitalized for road traffic crash injury to fatally injured drivers. Drug exposure assessment was heterogeneous, mostly depending on available retrospective data or on the molecule selection for biological testing.

Another identified issue was related to potential confounding. Particularly, alcohol or illicit drugs interact with medicinal drugs in impairing driving abilities and were not always taken into account. Driving conditions such as weekday, time of the day, road environment are important factors too, so is the number of miles driven. These latter factors were rarely assessed and included in risk modelling. Finally, the main issue of confounding by indication is addressed in a few studies only. Consequently, it often remains unclear whether crashes occur as a result of medicinal drug consumption or of the underlying disease, a concern highlighted in a literature review on benzodiazepines and driving [38].

This systematic review highlights several fields where more epidemiological data are needed. There is a need for large studies, investigating the individual and combined role of substances in the risk of road traffic crashes. The differential effect of the older generations of medicinal drugs versus newer ones must be compared to adapt patient care. The impact on crash risk of dose changes, beginning or end of treatment, must be further investigated. As described above, some non-psychoactive medicinal drugs may alter driving abilities due to their action on physiological functions or regarding central side effects. The impact of these medicinal drugs on road traffic crash risk has hardly been assessed in epidemiological studies so far. Other studies should also be designed to assess the relative roles of disease and medication in the risk of road traffic crashes. Quantifying the risk in patients who may be under-represented in the general driving population is also of interest as they may be at high risk due to the disease itself, and to the medicinal drugs used to treat the condition (eg Parkinson's disease and dopamine agonists [39]).

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Engeland *et al*, 2007 [12] Norway	Cohort Apr 2004-Sept 2005	3.1 millions 18-69 years old	Registry Crash with personal injury	Registry Exposed: - 7 or 14 days starting the day after dispensing - number of DDDs dispensed Unexposed: - unexposed or not previously exposed to the drug or to any prescribed drug	Age Gender Other prescribed drugs	natural opium alkaloids BZD tranquilizers BZD hypnotics NSAIDs	SIR=2.0 [1.7-2.4] SIR=2.9 [2.5-3.5] SIR=3.3 [2.1-4.7] SIR=1.5 [1.3-1.9]	Good
Gustavsen *et al*, 2008 [14] Norway	Cohort Jan 2004-Sept 2006	3.1 millions 18-69 years old	Registry Crash with personal injury	Registry Exposed: - 7 or 14 days starting the day after dispensing - incident use: washout period=180 days - concurrent use allowed or not Unexposed: - to the drug or to other prescribed psychoactive drugs	Age Gender Other prescribed drugs	zopiclone + zolpidem nitrazepam flunitrazepam	SIR=2.3 [2.0-2.7] SIR=2.7 [1.8-3.9] SIR=4.0 [2.4-6.4]	Good
Bramness *et*	Cohort	3.1 millions	Registry	Registry	Age	carisoprodol	SIR=3.7 [2.9-4.8]	Good

al, 2007 [9] Norway	Apr 2004- Sept 2005	18-69 years old	Crash with personal injury	Exposed: - prevalent use: exposure within 7 days starting the day after dispensing - incident use: washout period=180 days - concurrent use allowed or not - DDD Unexposed: - within the study period - within the washout period	Gender Other prescribed drugs	diazepam salbutamol	SIR=2.8 [2.2-3.6] SIR=1.1 [0.6-1.8]	
Bramness *et al*, 2008 [29] Norway	Cohort Apr 2004- Sept 2006	3.1 millions 18-69 years old	Registry Crash with personal injury	Registry Exposed: - prevalent use: any exposure within study - incident use: washout period=180 days - DDD Unexposed: - within the study period - within the washout period	Age Gender	Cyclic, sedating antidepressants Newer, nonsedating antidepressants	SIR=1.4 [1.2-1.6] SIR=1.6 [1.5-1.7]	Average
Neutel et al, 1995 [21]	Cohort 1979-1986	323,658 > 20 years old	Registry Hospitalization for	Registry Exposed:	Age Gender	BZD hypnotics BZD anxiolytics	OR=6.5 [1.9-22.4] OR=5.6 [1.7-18.4]	Average

Saskatchewan, Canada			crash injury	- incident use: washout period=6 months Unexposed: Absence of a prescription in the 6 months before simulated index prescription	History of alcohol abuse Other prescribed drugs			
Neutel, 1998 [28] Saskatchewan, Canada	Cohort 1979-1986	323,658 > 20 years old	Registry Hospitalization for crash injury	Registry Exposed: - incident use: washout period=6 months - repeat users: 3 prescriptions within 5 months Unexposed: Absence of a prescription in the 6 months before simulated index prescription	Age Gender Other prescribed drugs	BZDs Triazolam Flurazepam Oxazepam Lorazepam Diazepam	OR=3.1 [1.5-6.2] OR=3.2 [1.4-7.3] OR=5.1 [2.3-11.6] OR=1.0 [0.3-3.7] OR=2.4 [1.0-6.3] OR=3.1 [1.4-6.5]	Average
Ray *et al*, 1992 [22] Tennessee, USA	Cohort + Case-crossover 1984-1988	16,262 65-84 years old	Registry Crash with personal injury	Registry -current use (dose and duration) - indeterminate use - former use - non use	Age Gender Race Residence Year Use of medical care Non-psychoactive	BZDs cyclic antidepressants antihistamines opioid analgesics	RR=1.5 [1.2-1.9] RR=2.2 [1.3-3.5] RR=1.2 [0.6-2.4] RR=1.1 [0.5-2.4]	Good

					drugs			
Barbone *et al*, 1998 [8] Tayside Region, UK	Case-crossover 1992-1995	410,306 ≥ 18 years old	Registry 19 386 drivers involved in a first road-traffic crash	Registry Exposure assessment: dose and duration	All fixed characteristics Crash characteristics	tricyclic antidepressants selective serotonin-reuptake inhibitors BZDs zopiclone	OR=0.93 [0.72-1.21] OR=0.85 [0.55-1.33] OR=1.62 [1.24-2.12] OR=4.00 [1.31-12.2]	Good
Leveille *et al*, 1994 [17] Puget Sound, USA	Case-control 1987-1988	234 cases 447 controls ≥ 65 years old	Registry Cases: treatment for motor vehicle crash within 7 days of crash Controls: no crash injury during one year	Registry Exposure assessment: - probability quotient (quantity/days) - current use: within 60 days - past use: within 2-6 months - number of psychoactive prescribed drugs within 6 month	Age Gender Residence Chronic disease score and medical history Driving habits Race Marital status Education Diabetic receiving treatment	BZDs antidepressants opioids antihistamines	OR=0.9 [0.4-2.0] OR=2.3 [1.1-4.8] OR=1.8 [1.0-3.4] OR=0.7 [0.3-1.7]	Outstanding
Etminan *et al*, 2004 [13] Quebec	Case-control nested within a cohort Jun 1990-May 1993	5579 cases 13,300 controls 67-84 years old	Registry Cases: drivers in crashes with at least one personal injury Controls: random sample of the cohort	Registry Exposure assessment: - any use the year before - number of prescriptions - current use: within 60 days	Age Gender Residence Previous crash Other prescribed drugs Chronic disease score	Lithium carbamazepine	Rate Ratio=2.08 [1.11-3.90] Rate Ratio=0.83 [0.48-1.44]	Good
Delaney *et al*, 2006 [10]	Case-control nested within a	5579 cases 12,911	Registry Cases: drivers in	Registry Exposure assessment:	Age Gender	warfarin	Rate Ratio= 0.74 [0.55-1.05]	Good

Quebec	cohort Jun 1990- May 1993	controls 67-84 years old	crashes with at least one personal injury Controls: random sample of the cohort	- any use in the 30 days before - any use in one year - frequent use: ≥ 5 prescriptions	Residence Previous crash Chronic disease score Other prescribed drugs CV events and strokes			
Hemmelgarn *et al*, 1997 [15] Quebec	Case-control nested within a cohort Jun 1990- May 1993	5579 cases 55,790 controls 67-84 years old	Registry Cases: drivers in crashes with at least one personal injury Controls: random sample of the cohort	Registry Exposure assessment: duration of treatment New use: washout period=3 days	Age Gender Residence Previous crash Other prescribed drugs Chronic disease score	long half-life BZDs short half-life BZDs	Rate Ratio= 1.45 [1.04-2.03] Rate Ratio= 1.04 [0.81-1.34]	Good
Hemmelgarn *et al*, 2006 [25] Quebec	Case-control nested within a cohort Jun 1990- May 1993	5579 cases 13,300 controls 67-84 years old	Registry Cases: drivers in crashes with at least one personal injury Controls: random sample of the cohort	Registry Exposure assessment: - use during the one-year time window preceding - current exposure: use during the 30 days before - DDD and dose response	Age Gender Residence Previous crash Chronic disease score Other prescribed drugs	Insulin alone oral hypoglycaemics alone Insulin + oral hypoglycaemics Sulfonylureas Metformin Sulfonylureas + metformin Sulfonylureas + metformin	Rate Ratio= 1.4 [1.0-2.0] Rate Ratio= 1.0 [0.9-1.2] Rate Ratio= 1.0 [0.5-2.0] Rate Ratio= 1.0 [0.8-1.1] Rate Ratio= 1.0 [0.7-1.6] Rate Ratio= 1.3 [1.0-1.7] Rate Ratio=	Good

						(high dose)	1.4 [1.0-2.0]	
Skegg *et al*, 1979 [23] Oxford, UK	Case-control Mar 1974-Feb 1976	57 cases 1425 controls	Registry Cases: hospital admissions or deaths for injuries due to crash Controls: randomly selected from the same practice	Registry Exposure assessment: Medicinal drugs dispensed in the 3 month before	Age Gender Residence	sedatives and tranquilizers minor tranquilizers	RR=5.2 [2.2-12.6] RR=4.9 [1.8-13.0]	Average
Movig *et al*, 2004 [20] Netherlands	Case-control May 2000-Aug 2001	110 cases 816 controls	ER Cases: injured car or van drivers Controls: randomly selected from moving traffic	Urine/blood samples	Age Gender Blood alcohol concentration Other prescribed drugs Season Time of day	BZDs opiates	OR=5.05 [1.82-14.04] OR=2.35 [0.87-6.32]	Average
Honkanen *et al*, 1980 [16] Helsinki, Finland	Case-control 1977 (16 weeks)	201 cases 325 controls	ER Cases: injured drivers in ER within 6 hours Controls: randomly selected in petrol stations	Blood samples + interview	Weekday Hour of day Location	diazepam	found more commonly in patients than in controls p=0.03	Average
BZDand driving collaborative group, 1993 [24]	Responsibility May 1989-July 1990	3147 subjects 2852 complete files > 16 years old	Hospital centres Injured drivers examined less than 6h after the	Blood samples	Age Gender Alcohol	BZDs	No association	Average

France			crash					
Mura *et al*, 2003 [27] France	Case-control Jun 2000-Sept 2001	900 cases 900 controls	ER Cases: involved in a non-fatal road crash Controls: having a driving licence and attended for any non-traumatic reason	Blood and urine (or sweat) samples	Age Gender	Opiates (licit and illicit) BZDs	OR=8.2 [2.5-27.3] OR=1.7 [1.2-2.4]	Average
Jick *et al*, 1981 [26] Seattle, USA	Responsibility Jan 1977-Dec 1978	244 people with an automobile crash 15-64 years old	Registry Hospitalization for injurious car crash	Registry Exposure assessment: At least one prescription within 3 months	Age Gender	Sedating drugs	No association	Poor
Longo *et al*, 2000 [18] South Australia	Responsibility Apr 1995-Aug 1995 Dec 1995- Aug 1996	2500 non-fatally injured drivers	Hospital crash and emergency unit Non fatal road crashes victims who survive >30 days	Blood samples	Alcohol and illicit drugs	Benzodiazepines	Significant increase in culpability	Average
Drummer *et al*, 2004 [11] 3 states of Victoria, Australia	Responsibility 1990-1999	3398	Registry Fatally-injured drivers	Forensic toxicology	Age Gender Alcohol and illicit drugs Type of crash Location	BZDs Opiates (licit and illicit) Other psychoactive medicinal drugs	OR=1.27 [0.5-3.3] OR=1.41 [0.7-2.9] OR=3.78 [1.3-11]	Good

					Year			
McGwin *et al*, 2000 [19] Alabama, US	Responsibility + Case-control 1996	901 drivers ≥ 65 years old	Registry Responsibility: subjects involved in at least one automobile crash Case-control: comparison with drivers not involved in crashes	Questionnaire	Age Gender Other prescribed drugs Annual mileage Associated diseases	BZDs antidepressants NSAIDs ACE inhibitors anticoagulants calcium channel blockers vasodilators oral hypoglycaemics insulin	OR=5.2 [0.9-30.0] OR=0.3 [0.1-1.0] OR=1.7 [1.0-2.6] OR=1.6 [1.0-2.7] OR=2.6 [1.0-7.3] OR=0.5 [0.2-0.9] OR=0.3 [0.1-1.0] OR=1.3 [0.7-2.4] OR=0.9 [0.4-1.8]	Average

DDD=defined daily dose, BZD=benzodiazepine, SIR=standardized incidence ratio, OR=odds ratio, RR=relative risk

Table 1: Epidemiological studies of traffic crash risk and medicinal drug consumption: methodology and main results

Appendix 1: Reading grid

Criteria	Y	I	N	NA	DNK	Comment
Study design						
Objectives are clearly stated	☐	☐	☐	☐	☐	
Key elements of study design are provided	☐	☐	☐	☐	☐	
Location and dates are specified	☐	☐	☐	☐	☐	
Participants						
Cohort study						
Eligibility criteria are defined and appropriate	☐	☐	☐	☐	☐	
Exclusion criteria are defined and appropriate	☐	☐	☐	☐	☐	
Sources are described and appropriate	☐	☐	☐	☐	☐	
Selection method is described and appropriate	☐	☐	☐	☐	☐	
Selection is independent from risk of collision	☐	☐	☐	☐	☐	
Follow-up period is defined and long enough	☐	☐	☐	☐	☐	
Compared exposures are described	☐	☐	☐	☐	☐	
Reference group is appropriate	☐	☐	☐	☐	☐	
Selection procedures are identical in all exposure groups	☐	☐	☐	☐	☐	
Case-control study						
Eligibility criteria are defined and appropriate	☐	☐	☐	☐	☐	
Exclusion criteria are defined and appropriate	☐	☐	☐	☐	☐	
Sources are described and appropriate	☐	☐	☐	☐	☐	
Selection is independent of drug exposure	☐	☐	☐	☐	☐	
Definition of cases is appropriate	☐	☐	☐	☐	☐	
Controls are selected from same population as cases	☐	☐	☐	☐	☐	
Control group is appropriate	☐	☐	☐	☐	☐	
Selection procedures are identical in cases and controls	☐	☐	☐	☐	☐	
Matching is appropriate	☐	☐	☐	☐	☐	
Variables						
Drug exposure						
Data sources are described and appropriate	☐	☐	☐	☐	☐	
Choice of studied drugs is justified	☐	☐	☐	☐	☐	
Drug exposure assessment method is described and justified	☐	☐	☐	☐	☐	

Case/control status is masked when assessing exposure	☐	☐	☐	☐	☐
Collision data					
Data sources are described and appropriate	☐	☐	☐	☐	☐
Collision characteristics are accounted for	☐	☐	☐	☐	☐
Accounting for potential confounders					
Age	☐	☐	☐	☐	☐
Gender	☐	☐	☐	☐	☐
Associated diseases	☐	☐	☐	☐	☐
Number of kilometres/miles driven	☐	☐	☐	☐	☐
Alcohol and other drugs	☐	☐	☐	☐	☐
Statistical methods					
Sample size calculation	☐	☐	☐	☐	☐
Appropriate estimates and models	☐	☐	☐	☐	☐
Control for confounding	☐	☐	☐	☐	☐
Sensitivity analysis	☐	☐	☐	☐	☐
Results					
Number of subjects reported	☐	☐	☐	☐	☐
Number of refusals reported	☐	☐	☐	☐	☐
Description of all groups	☐	☐	☐	☐	☐
Reported confidence intervals or p	☐	☐	☐	☐	☐
Discussion					
Key results/study objective	☐	☐	☐	☐	☐
Limitations and possible biases discussed	☐	☐	☐	☐	☐

(Y=Yes, I=Incomplete, N=No, NA= Not Applicable, DNK=Do Not Know)

Conclusion	
Quality	
Outstanding	☐
Good	☐
Average	☐
Poor	☐

Discussion