Effects of benzodiazepines, antidepressants and opioids on driving: a systematic review 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: The aim of this systematic review was to examine the association of 3 classes of commonly used psychoactive drugs (viz. benzodiazepines and newer non-benzodiazepine hypnotics, antidepressants and opioids) with 1) the risk of traffic accidents (as indexed by epidemiological indicators of risk) and 2) driving performance (as indexed by experimental measures of driving performance).

Methods: A literature search for material published in English 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 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) drivers (pooled OR: 1.13, 95% CI: 0.97 – 1.31) than in younger (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 daytime, impaired driving performance independent of their half-lives. As for hypnotics, converging evidence from experimental and epidemiological studies indicates that diazepam, flurazepam, flunitrazepam, nitrazepam and 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 (> 60 years) 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 acute 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 young 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 acute impairment in driving performance. Opioid users seemed to be at a higher risk of traffic accidents; however experimental evidence is scarce on their effects on driving. The clinical and medico-legal implications of these findings are also discussed.

1. 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 expected to carry out their daily activities in a similar manner to healthy 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.[see 1, 2 for reviews, 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

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not responsible for accidents. Therefore the present review also focuses on accident responsibility studies.

The aim of experimental studies is to determine the causative role of single or a few doses of drugs on driving performance as tested in different actual driving tests[e.g.5, 6, 7] or driving simulator tests.[e.g. 8, 9, 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 almost always 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 had been also validated against surrogate markers of traffic safety. For example, in a standardised driving test developed by O'Hanlon and colleagues in 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 interact with other vehicles, pedestrians, traffic signs and other roadside objects. According to cognitive models of driving, more complex processes necessary to interact with the external environment and make higher level decisions in driving are categorised as 'tactical' and 'strategic' level

processes.[11-13] Different actual and simulated driving tests have attempted to tap these higher level aspects of driving and are reviewed in the present paper.

Many recent epidemiological studies[e.g.17, 18, 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 also will focus down onto the level of individual drugs. In addition, we also focus on different subject factors (patients vs. healthy volunteers, young vs. old) that are likely to modify drug effects on driving and traffic accidents.

Objectives:

The broad objective of the present study was to systematically review the literature to find out whether three classes 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;

1) whether use of each of these drugs are associated with increased risk of traffic accidents (as indexed by risk estimates measured in analytical epidemiological studies) and

2) whether experimental administration of these drugs causes impairment in driving performance (as indexed by quantitative measures of driving performance in a real vehicle or a driving simulator).

2. METHODOLOGY

2.1. 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', 'antidepressant agent' and 'opiate agonist'. The second set included the EMTREE / MeSH terms 'traffic accidents', 'traffic safety' and 'car driving' and 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.

2.2. Inclusion criteria

Inclusion criteria for epidemiological studies were; a) cohort or case-control study design or variants such as case-crossover studies (survey designs and other descriptive studies were excluded) and b) 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 hospitalisation' 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; a) administration of a single dose or multiple doses of a relevant drug to at least one of the study groups and b) implementation of an actual driving test or a test in a driving simulator (studies that examined cognitive /

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psychomotor functions related to driving by laboratory tests were excluded). The

methodology of the experimental studies was evaluated under 4 categories: experimental

design, selection of study samples, pharmacological manipulation and outcome measures.

The initial search retrieved 1271 articles. Exclusion of the papers which did not meet

the inclusion criteria are summarised 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 1) and 8 were cohort studies (Table 2). Nineteen epidemiological studies

investigated exposure to benzodiazepines, 6 to antidepressants and 7 to opioids. Of the 69

experimental studies, benzodiazepines and/or 'z drugs' were tested in 48 studies

(Supplementary Table 1), antidepressants in 20 (Supplementary Table 2) and opioids in 3

(Supplementary Table 3).

2.3. 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 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.

3. RESULTS

3.1. 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 summarised with the limitations specific to individual studies noted in Tables 1 and 2, respectively.

Two distinct sampling methods can be observed in epidemiological studies. Seven case-control studies 'recruited' cases from drivers that were hospitalised[4, 20-23] or died[24, 25] after traffic accidents whereas controls were recruited either from the victims of traffic accidents or randomly from the roadside.[20, 22] Drug exposure was ascertained by analysing the blood or urine samples. The main advantage of this method is availability of confirmatory evidence for occurrence of the drug under question at the time of accident.

In other case-control studies (except one, where exposure was ascertained through an interview[26]) 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

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showed whether the patient was prescribed (and hence likely to be taking) the drugs at the time of 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. Firstly, 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 left-over 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. Secondly, only a certain percentage of the outcomes (i.e. traffic accidents) are recorded in the databases. Particularly less serious accidents, which is likely to represent a significant proportion of all accidents, might have not been entered. For example, studies that recruited accident victims from hospitals [4, 20-23] only includes injurious traffic accidents where the injuries were serious enough to seek medical assistance. Thirdly, data on some important confounders may have not recorded in the registries. Many studies did adjust the analyses or matched the samples for demographic variables (e.g. age, gender) 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 had left a certain degree of residual confounding. Other limitations and potential biases specific to individual epidemiological studies are noted in Tables 1 and 2.

3.1.1. 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, 1 case control study[27] and 2 cohort studies[18, 28] 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[22, 27] 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. The first was a case cross-over 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 accident date).[27] The adjusted OR for all benzodiazepines in this study was 1.62 (95% CI 1.24 - 2.12) suggesting higher accident risk associated with benzodiazepines use. The second study reported 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.[22]

The other six publications contained adequate data for analysis and were included in the meta-analysis (see Figure 2). 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. 2009 used the same set of studies. However, the authors included subject counts only for long-acting benzodiazepines in the Hemmelgarn et al. 1997 study in their analysis.[29] We included the subject counts for all benzodiazepines in Hemmelgarn et al. study because long / short-half-

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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 the subjects of the Leveille et al. 1994 study were exposed to triazolam).

2) *Cohort studies on benzodiazepine exposure and traffic accident risk* (Figure 3): Of the 6 cohort studies, two[18, 19] included the same data-sources used in a previous study[30] and thus those two articles were excluded. One other article was also excluded as it did not have enough information to calculate risk.[28] However, this study showed a significantly high incidence rate ratio (IRR) suggesting benzodiazepines are associated with increased traffic accident risk. The remaining three studies[30-32] were included in the meta-analysis (see Figure 3). Similar to case-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 benzodiazepines users (pooled IRR: 1.81, 95% confidence intervals: $1.35 - 2.43$).

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 due to inadequate data[27]; however this study showed a significant association between accident responsibility and benzodiazepine exposure. The other 5 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[25], information from police / researcher investigation findings[21] and comprehensive scoring systems based on drivers' attempts to mitigate an accident[4, 33] as well as subjective recall.[26] The last study

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was the smallest and had the widest confidence intervals.[26] 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 3 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. day-time 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. Firstly, we estimated the pooled ORs of the 3 case-control studies that only involved old (>65 years) drivers[26, 34, 35] and 3 case control studies that comprised drivers over a wider age range starting from 18 years.[20, 23, 36] There was no significant statistical heterogeneity among the studies once the studies were sub-grouped 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). Secondly, of the epidemiological studies that had participants across a wider age range, four have reported the age stratified risk estimates for traffic accidents.[19, 27, 30, 37] Of these, three report lower risk in older groups than in younger groups[19, 27, 30] while one reported similar ORs in the young (<60 years) and the old (>60 years).[32] One accident responsibility study

also report age-stratified risks, and found higher responsibility in young benzodiazepine users but not in their older counterparts.[25]

Therapeutic use and dosing regimen:

Anxiolytics are taken usually in single or multiple doses in daytime and thus it is possible that they increase accident risk irrespective of their short half-lives. Two cohort studies and one case-control study have categorised benzodiazepines as anxiolytics or hypnotics. All 3 showed increased risk with anxiolytics.[27, 30, 32] Two cohort studies showed an increased risk in the groups using hypnotics[30, 32] while the case control study showed that as a group, hypnotics did not significantly increase traffic accident risk.[27] 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[34] and the other on accident responsibility.[25] The first study categorised benzodiazepines into short (≤ 24 hours) and long elimination half-life (> 24 hours) drugs.[34] Long-half-life drugs but not short-half-life drugs were associated with increased accident risk in the elderly. The second categorised benzodiazepines into short (< 6 hours, mainly midazolam), intermediate (6-12 hours) and long elimination half-life (>24 hours) drugs.[25] New users of long-half-life 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 to controls.

Where individual drugs have been analysed, the accident risk is increased with the use of diazepam[19, 28, 32] even after 2-4 weeks into treatment, but not with oxazepam.[32] Alprazolam was also more commonly detected in drivers responsible for accident than in

those who were not responsible.[25] 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. Long-acting benzodiazepines flunitrazepam,[18] flurazepam [32] and nitrazepam[18, 28] appear to increase the risk of traffic accidents. However, medium-half-life benzodiazepine hypnotics lorazepam[32] and temazepam[28] and short-acting benzodiazepines triazolam[32] were also found to increase the accident risk. No significant effect was observed with very-short acting hypnotic midazolam.[25] The short acting non-benzodiazepine hypnotic zopiclone was examined in 3 studies. One case-control study shows a 4-fold increase in accident risk[27] while a large scale cohort study reports a 2-fold increase in accident risk.[18] The other study did not show a significant change in the accident risk with zopiclone.[28] For the short-acting hypnotic zolpidem, the large-scale study reports a two-fold increase in risk[18] while the other report no significant effect.[28]

Duration of use:

Five cohort studies have examined the traffic accident risk of benzodiazepines during the first 1-4 weeks after prescription and all found increased risk of traffic accidents.[18, 28, 30, 32, 38] Two studies reported that the risk remained high with continuing use.[28, 34]

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[27, 31] 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.

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3.1.2. Antidepressants

Antidepressants were examined in 3 case-control studies and 3 cohort studies. One study, where all antidepressants were considered as a single group did not show a significant increase in traffic accident risk,[32] or accident responsibility.[26] 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 show no significant increase in accident risk either with tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs)[27, 28] while one reports an increased risk with both sedative and non-sedative antidepressants.[38] 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,[31, 35] with one study demonstrating that the risk increases with dose.[31] 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.

3.1.3. Opioids

Risk of traffic accidents associated with prescription use of opioids has been examined in 4 cohort studies and one case control study. Of the 4 cohort studies, 2 had overlap of data sources[17, 30] and one did not have adequate information to calculate risk.[28] 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.[28, 30] The effect on accidents in elderly drivers (>65 years) is

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inconsistent.[22, 35] Limited evidence suggests that codeine,[17, 28] dihydrocodeine[28] and tramadol[28] 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[22] nor accident culpability.[33]

3.1.4. Drug-alcohol interactions and drug interactions

Drug-alcohol interactions are reported in 3 case-control studies. Benzodiazepine-alcohol combinations always showed a greater risk of traffic accidents[22] and accident culpability.[4, 21] 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 1). 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 times (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 3 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 30% increase in the accident risk, which further increased to 100% with the use of two or more drugs.[35] Similarly, the cohort study showed 110% increase in traffic accident risk if the driver is on both benzodiazepines and TCAs.[31]

3.2. EXPERIMENTAL STUDIES: EFFECTS OF BENZODIAZEPINES, ANTIDEPRESSANTS AND OPIOIDS ON DRIVING PERFORMANCE

3.2.1. Appraisal of the methodology:

Any methodological concerns specific to each study are noted against the respective studies in Supplementary Tables 1-3. Table 3 summarises the different methodological approaches of the 69 experimental studies.

3.2.1.1. Experimental design

Of the 69 studies, 63 were double-blind placebo-controlled studies whereas 6 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 minimise systematic changes in performance across treatment conditions by providing adequate practice to participants and by randomising treatment order. The participants were assigned into separate treatment or placebo groups in the other 6 double-blind placebo-controlled studies (3 randomized, 3 not specified).

Of the 6 experimental studies with other designs, the participants were patients in 4 studies.[39-42] Single groups of patients were tested before and after treatment in two of these studies, whereas a control group treated with an active drug were included in the other two. The remaining two studies where healthy volunteers were tested, one was a randomised double-blind study in which lorazepam served as an 'active-control' drug[7] whilst the other one was a non-blind study.[43]

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3.2.1.2. Study samples

The 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 suffering from insomnia,[5, 44-49] anxiety,[50-52] depression[39, 42] and chronic pain.[41, 53]

Participants of almost all experimental studies were relatively young. Of the 69 studies, only four[54-57] had elderly participants.

3.2.1.3. Pharmacological manipulation

Driving performance was tested after one or 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 wash-out periods were ensured between treatment conditions in all crossover studies.

The driving impairment observed in drug naïve individuals with fixed, single / short-term dosing regimes 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 on 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 naïve subjects in experimental studies.

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3.2.1.4. 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 standardised highway driving test developed by a research group in The Netherlands had been used in 31 experimental studies retrieved in the current review.[5 for technical details] The primary aim of the driving task is to maintain a constant lateral position and constant speed of 95km/h. The main outcome measure, 'standard deviation of lateral position (SDLP)' indicates the degree of weaving of 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, 50, 58-61] Brake reaction time was an outcome measure in 7 studies on actual driving.[58, 62-66] 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-the-road driving. Some simulator studies have measured mean variance of lateral position and mean variance of speed which are comparable with SDLP and SDS, respectively. However there are two main limitations in predicting actual driving performance based on simulated driving. Firstly, the artificial

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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 simulators 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, 67-69] whereas the most complex simulator tests employed more life-like driving scenarios and emulated the forces acting upon an actual moving vehicle.[43] Secondly, 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.[29] The authors report nightly doses equivalent to ≤ 5mg of diazepam significantly increase SDLP the following morning but not in the following afternoon. Doses equivalent to 10mg or more of diazepam 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, 70, 71] 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 0.1g/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

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driving studies. Thus the present review on experimental studies evaluates the effects of individual drugs on both actual and simulated driving tests.

3.2.2. Benzodiazepines and 'z' drugs

All 49 studies that we retrieved administered benzodiazepines orally in therapeutic doses. The doses were generally equivalent to 10-20mg of diazepam in almost all studies. Lower doses have been used in a few studies: diazepam 5mg-7mg in two,[43, 72] nitrazepam 5mg in one[59] and lorazepam 0.5mg in one.[52] Two different dosing regimens which 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 half-an-hour to about 5 hours after dosing. Hypnotics were always administered at night (replicating their therapeutic use) and driving was tested in the following morning (9-10 hours after dosing) or afternoon (16-17 hours after dosing).

3.2.2.1. Benzodiazepine anxiolytics

The results obtained in our search include 5 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.[67] Acute increase in SDLP[72] and brake reaction time[62] has been observed after a 10mg dose in on-the-road driving tests. A single 5mg dose did not cause a significant increase in SDLP in healthy volunteers,[72] but did increase with thrice daily dosing.[52] The impairing effect of the latter dosing regimen was observed up to 7 days in healthy volunteers[52] and up to 3 weeks in patients with anxiety.[51] These observations suggest that even administered in low doses, repeated administration of long-acting benzodiazepine like diazepam may cause significant

impairment. In driving simulator tests, 10-15 mg doses caused increased collisions,[9] increased tracking errors and reaction times[67, 69] and impairments in composite measures of overall driving performance.[54, 73] 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 0.11mg/kg body weight (~7mg) or 0.22mg/kg body weight (~15mg).[43] 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 inter-subject variability in driving performance in this study probably attributable to the complex driving task and relatively short practice session and 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 week of continuing treatment. These findings are consistent with the epidemiological evidence that showed increased accident risk in diazepam users.[19, 28, 32]

Lorazepam: Lorazepam was tested in 5 studies. SDLP was the outcome measure in 3 experiments and all showed a significant increase with lorazepam even after 1 week of treatment.[52, 74] Of these, one study was on a group of patients with anxiety and the experimenters continued treatment for 2 weeks and found a significant impairment even at the end of this period.[52] 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, 58]

Alprazolam: The 2 studies on *alprazolam* showed a 1mg dose can severely impair highway driving performance as indexed by SDLP.[75, 76] Sustained-release preparation of the drug caused less impairment but was still significant.[76]

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Clobazam: No significant acute impairment was detected in different driving manoeuvres after 3 days of treatment with 10mg t.i.d.[62] or after 20mg morning.[58] 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.[50]

3.2.2.2. Benzodiazepine 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 6 driving performance studies and all report impairment with the drug. One to 2 days of treatment caused a significant increase in SDLP and SDS that lasts up to 10-11 hours after dosing in healthy volunteers with 30mg, and up to 16-17 hours in patients with insomnia after 15-30mg.[5, 46] One study on patients showed the following morning's impairment was persistent even after 1 week of continuing treatment.[46] Another actual driving experiment found impaired manoeuvring skills in a slalom task 12 hours after a 15mg dose.[61] Driving simulator tests showed increased tracking error and brake reaction time and reduced speed of driving.[10, 77] These findings are consistent with the Neutal et al. 1995 study where flurazepam was associated with a 5-fold increase in the risk of injurious traffic accidents.[32]

Flunitrazepam (half-life: 18-26 hours. Active metabolite: 36-200 hours) : A single 2mg dose of flunitrazepam did not affect the SDLP after 10 hours in a group of young patients with sleep disturbances in one study,[47] but did cause a significant increase which lasted 16-17 hours after 2 doses in another.[5] This may be due to accumulation of this long-half-life benzodiazepine. In line with these findings, another on-the-road driving study

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showed impaired steering control which lasted after 7 days of treatment in a group of patients with insomnia.[45] Of the three driving simulator studies, one also reports increased lateral deviation and speed variation 10 hours after 1mg dose.[78] 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 2 studies. A10mg dose increased SDLP which was observed 16-17 hours after a nocturnal dose in a group of young women with insomnia.[44] This impairment persisted even after 8 days of continuing treatment. This evidence supports the epidemiological findings where nitrazepam was associated with 170% increase in traffic accidents in the first week of use.[18] A lower dose (5mg) 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.[59]

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

Temazepam (8-22 hours): All 5 studies that tested the effects of temazepam used 20mg nightly doses. SDLP was not significantly affected either in healthy elderly volunteers after a single dose[79] or in young women with insomnia who received 3 consecutive doses[44] the following morning (i.e. 10 hours after dosing). Two other driving studies reported that the drug did not impair manoeuvring ability in healthy volunteers[61] or steering control in young insomniacs[45] 10-12 hours after a single or multiple doses. Interestingly, temazepam also did not affect lateral position, speed deviation or reaction time in a group of elderly volunteers, even if they were tested only 5.5 hours after a 2am dose.[48] However one cohort study shows that temazepam is associated with increased traffic accident risk during the first four weeks of use and to a lesser extent, during an extended period of use.[28]

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Loprazolam (6-12 hours): The only study on *loprazolam* (1mg and 2 mg) shows impairment in highway-driving (as measured by SDLP) even 16-17 hours after 2 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 5 experimental studies. Lorazepam 1mg or 2mg administered at night did not have significant acute or subchronic effects in the morning on SDLP in patients with insomnia.[46] Healthy volunteers showed a significant impairment 10 hours after the first two days of administration but not 16 hours after the second dose.[68] In driving simulation experiments lorazepam 2mg increased tracking errors and reaction time when tested 1-5 hours,[67] but did not have significant acute[10, 68, 80] or subchronic[10] effects when tested in the morning following a nightly dose.

Short-acting hypnotics which 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 0.25mg,[69] but no significant effects were observed on simulated driving when tested in the morning following a 0.25mg or 0.5mg nightly doses.[59, 77] However, given that there is some evidence that triazolam may be associated with increased accident risk,[32] it is worth investigating drug effects also with on-the-road driving tests.

Midazolam (half-life: ~ 2 hours): The only study on midazolam did not show a significant impairment in brake reaction time 10 hours after *midazolam* 15mg.[63]

Zopiclone (half-life: 5-6 hours): Effects of zopiclone have been tested in 4 standardised on-the road driving studies and 5 driving simulator experiments. All studies used the standard treatment dose of 7.5mg. Despite the short-half life of the drug, there is consistent evidence that SDLP increases 5 hours[81] and 10 hours after a bedtime dose in healthy young volunteers[79, 81, 82] and 10 hours post-dose in the elderly individuals.[56] One driving simulator study also reported increased lateral position deviation 10 hours after dosing but not after 12 hours.[78] Other driving simulator studies reported increased collisions after 9-11 hours,[49] increased tracking errors after 1.5 hours[69, 83] and delayed brake reaction time after 1.5 and 4.5 hours.[69] These findings parallel the markedly high traffic accident risk associated with zopiclone in epidemiological studies.[18, 27] This is an unexpected trend given the short plasma half-life of zopiclone.

Zolpidem (half-life: ~ 2 hours): Two actual driving study and 1 simulator study examined the effects of zolpidem 10mg 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[79, 84] and increased the variance of lateral position in patients with insomnia in the simulator study.[48] Similarly, increased poor lateral position and speed control were reported at 2 hours, but not 13 hours after a 10mg dose in another driving simulator study.[85] One actual driving study and 2 simulator studies showed that zolpidem 10mg does not impair SDLP in young insomniacs,[47] or mean lateral position variance in healthy elderly[78] or young insomnia patients,[49] when tested in the following morning (i.e. 9-10 hours post-dose). The experimental evidence indicates that a 10mg bedtime dose of zolpidem does not affect the basic control processes of driving in the following morning but does impair if taken in the middle of the night. The largest cohort study conducted so far reports a two-fold increase in traffic accident risk in young zolpidem users during first 4 weeks of use,[18] while another did not find a significant increase in the risk.[28] However, the exposure was based on

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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 in 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 had been examined only in 3 on-the-road driving studies. They showed that SDLP or SDS in healthy young individuals are not affected by 10 or 20 mg dose when tested 10 hours (i.e. morning after a bedtime dose)[82, 84] or 4-5 hours (i.e. middle of the night dose).[81, 84]

Eszopiclone (half-life: 6 hours): According to the 2 driving experiments conducted so far, eszopiclone 3mg did not affect the brake reaction time in either healthy young or elderly individuals, when tested 9-19.5 hours post-dose.[66]

3.2.3. Antidepressants

Antidepressants have been used in therapeutic doses in almost all studies. Driving performance has been tested 1-5 hours after dosing, except in 5 studies[42, 86-89] where drugs were given at night and driving was tested on the following morning.

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

3.2.3.1. Sedating antidepressants

Amitriptyline: Effects of amitriptyline have been examined in 4 actual driving experiments and 4 simulated driving tests. Three showed acute increase in SDLP after 25mg[5, 88] and 75mg.[90] A comparable driving simulator experiment found increased SDLP and headway variability 4 hours after amitriptyline 25mg,[91] with a moderate positive

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correlation between plasma amitriptyline concentration and SDLP.[8] Only one study tested driving on the following morning after nocturnal dose. [88] The investigators found increased SDLP even 13 hours after a 25mg nocturnal dose in patients with neuropathic pain. The other 4 studies report impaired tracking / steering control[69, 92, 93] and brake reaction time[69, 94] 2-5 hours after a 50mg 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 50mg b.i.d.,[95] doxepin 25mg t.i.d.,[5, 96] mianserin 10mg t.i.d.[5, 96, 97] Three studies on the effects of nocturnal doses showed that SDLP was increased in the following day (13-17 hours post-dose) with mirtazepine 15mg[89] and 30mg,[87] but not after dothiepin 75mg[86] or mianserin 30mg.[89] The only experimental study on elderly participants show no acute effects (2 hours post-dose) of imipramine 50mg on SDLP, although a significant increase was observed in their younger counterparts.[55]

Effects of continuing treatment: Post-dose impairment in SDLP remained significant even after 1-2 weeks of treatment with mianserin,[96, 97] but not with imipramine,[95] doxepin,[96] mirtazepine[87] or amitriptyline.[88, 90] Only 3 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.[53] The other two driving simulator studies on depressed patients showed improvement of performance after two to four weeks of treatment with mirtazepine.[39, 98] The latter study also found that performance did not improve in an untreated control group.[98]

3.2.3.2. 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 standardised 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 SSRIs paroxetine (10mg),[91] fluoxetine (20mg)[86] and escitalopram (10-20mg),[87] serotonin-noradrenaline reuptake inhibitor venlafaxine (37.5-75mg b.i.d.)[97] and monoamine oxidase inhibitor moclobemide (200mg b.i.d.).[96] The only study on depressed patients reports that driving performance (as tested on a simulator) improves after a two-week treatment with non-sedating antidepressant reboxetine as well as with sedative antidepressants mianserin.[39]

3.2.4. Opioids

Only 3 experimental studies examined the effects of opioids on driving (Supplementary Table 3). One study on healthy volunteers showed increased collisions in a driving simulator task after a single 50mg dose of codeine[99] while the other showed no significant acute effects of oxycodone-paracetamol combined preparation (5mg/325mg and 10mg/650mg) on SDLP or SDS.[100] 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 to 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.[41] There was no significant change in performance as assessed with a driving simulator test.

3.2.5. 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,[67] flurazepam,[77] triazolam[69] and amitriptyline.[93]

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.[69]

4. DISCUSSION

The present paper reviewed 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 account 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 60-80% increase 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 presence of alcohol and benzodiazepines was associated with 7.7-fold increase in the risk of 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 0.5-0.8g/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 with lower doses of benzodiazepines compared to their younger counterparts. Perhaps elderly drivers on benzodiazepines may appreciate the potential deleterious effects of drugs more and resort to safer driving patterns or limit driving while they are on 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 elderly[54, 56, 57] and they do not make a clear distinction between drug effects on young and the elderly. Although driving experiments in elderly drivers after sedative drugs may have safety and ethical concerns, further research on 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 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.

The 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 up to the following afternoon in 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 2-3 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 0.05-0.08g/dL,[101, 102] which is above legal limits for driving in most countries. A series of on-the-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 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 prescribed diazepam should be strongly encouraged not to drive at least during the first four weeks of treatment. However, unlike

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with 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.[27,28,38] 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. As the antidepressants do not bring therapeutic effects immediately after commencement of treatment, patients may show driving impairment irrespective of the sedative properties of the antidepressants during the first 1-2 weeks of treatment. Patients on sedative antidepressants may be affected more than those on non-sedating antidepressants during this initial stage due to acute sedative effects of the drugs, as has been observed in healthy volunteers in experimental studies. Continuing treatment beyond 3-4weeks 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 notion is supported by limited experimental evidence which showed that young patient groups treated with sedative or non-sedative antidepressants improved their driving skills after a few weeks[39, 88, 98] while untreated patients did not.[98] 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 [27] and self-controlled case-series [28] studies have attempted to

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overcome this methodological constraint by employing with-in 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 suggests that opioid users (at least in young drivers) may be at a 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 under treatment. Similar to 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[22,27,28] in the meta-analyses as they did not contain the necessary information required to calculate risk estimates which are compatible with the majority of the studies. However, only the magnitudes of the risk estimates of these studies were different from the pooled estimates; the direction of association was the same. It has to be also admitted 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, epidemiological studies showed that some 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.[103]

5. 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 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

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performance over the course of treatment in depressed patients. Opioid users seem to be at a

higher risk of traffic accidents; however experimental evidence is scarce on their effects on

driving.

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Table 1: Case control studies (OR: Odds ratio, RR: Relative risk, SIR: Standardised incidence ratio, TA: Traffic accident)

Study, Country	Design, period	Study population from which the 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., 1979 [36] UK	Matched case-control, Mar 1974 – Feb 1976	43,117 people registered with 16 general practitioners	57 drivers died or hospitalised due to injuries from TA	1425 randomly selected people from GP registers	Prescription records: Prescribed and dispensed with a tranquilliser within 12 weeks before TA	matched for sex, general practice enrolled, year of birth	All tranquilisers Minor tranquillisers Major tranquillisers	RR=5.2 (2.2 – 12.6) RR=4.9 (1.8 – 13.0) RR=6.9	No confidence interval given for major tranquillisers as there were too few subjects
Honkanen et al., 1980 Helsinki, Finland [20]	Case-control, Apr, May, Sept, Oct 1977		201 drivers arrived at emergency department within 6h after TA	325 car drivers selected randomly at petrol stations	Serum analysis for benzodiazepines	matched for weekday, hour of day and location of accident	Benzodiazepines (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., 1981 Puget Sound, US [104]	Case control, Jan 1977 – Dec 1978	Patients (15-64y) 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 tranquilliser, antihistamines or narcotic analgesic) within 3 months of accident.	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 1) questionable accuracy of clinical notes in assigning at-fault status of drivers. 2) no adjustment for alcohol (more cases drinking than controls). 3) no direct comparison of drivers at fault and not at fault.
Lagier et al., 1993 France [21]	Case-control May 1989 – July 1990	Patients admitted to hospital after TA injury	Drivers responsible for accident	Drivers not responsible for accidents and pedestrians	Blood analysis for benzodiazepines		Blood Alcohol <0.2g/l Blood alcohol >0.2g/l Blood alcohol 0.2-0.8g/l with no benzodiazepines	OR = 0.96 (0.8– 1.2) OR = 7.2 (3.4 – 15.2) OR = 2.03 (1.4 -2.9)	Benzodiazepine-alcohol combination increases risk compared to alcohol / benzodiazepine alone.
Leveille et al., 1994 Puget Sound, US [35]	Matched case-control 1987-1988	Enrolees of Group Health Corporative, Puget Sound	234 drivers >65yrs old, sought treatment for MVC within 7days of accident	447 Drivers >65yrs old matched for age, sex, county of residence, but not met with MVC during the	Prescription records Current exposure: prescription within 60 days Past exposure: prescription 60days– 6 months	Race marital status, education miles driven, insulin or oral hypoglycaemic use for	Benzodiazepines: Current exposure Past exposure Cyclic antidepressants: Current exposure Past exposure	OR = 0.9 (0.4 – 2.0) OR = 1.2 (0.5 – 2.7) OR = 2.3 (1.1 – 4.8) OR = 0.7 (0.2- 1.9)	Main benzodiazepine triazolam (~50%). Exposure status was defined in relation to a given class of drugs. 'Unexposed group' may have been exposed to

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Study	Design, period	Population	Cases	Controls	Exposure	Confounders	Drug category	OR	Comments
				same calendar year	before No exposure: no prescriptions within 6 months	diabetes	Opioids: Current exposure; Past exposure; Number of drugs in current users; One type; >= 2 types	OR = 1.8 (1.0 – 3.4); OR = 1.0 (0.5 – 1.8); OR = 1.3 (0.8 – 2.0); OR = 2.0 (1.0 – 4.0)	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.
Hemmelgarn et al., 1997 Quebec, Canada [34]	Nested case-control, June 1990 – May 1993	67 – 84 year old subjects who pocessed a valid driving licence and resided in Quebec for at least 2 years	5579 drivers involved in injurious crashes	55790 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 benzodiazepine use within 365 days preceding index date	Sex; Age; Locality of residence; History of previous injurious MVC; Chronic disease score; Use of other CNS drugs	Long-half-life benzodiazepines: Current use; 1st week of use; Short-half-life benzodiazepines: Current use; 1st week of use	OR=1.28 (1.12-1.45); OR=1.45 (1.04-2.03) OR remains high in first year of use.; OR=0.96(0.88-1.05); OR=1.04(0.81-1.34)	Long t ½: clonazepam, diazepam, clorazepate, flurazepam, nitrazepam, chlordiazepoxide. Short t ½: alprazolam, bromazepam, lorazepam, oxazepam, temazepam, triazolam
Barbone et al., 1998 Tayside, UK [27]	Case-crossover, Jan 1992 – Jan 1995	410306 residents in Tayside Region, UK, and who had been registered with a Tayside general practitioner	19386 persons >= 18y of age, who experienced an TA Case period: The day of TA	Control period: Same day of the week in preceding 18 weeks	Intake of the drug on the day based on dispensed prescription records.	Stratified for Age; Sex; Severity of injury; Breath alcohol; Lighting; Driver culpability	Benzodiazepines: All; Anxiolytics; Hypnotics; Zopiclone; TCAs; SSRIs	OR=1.62 (1.24-2.12), Higher risk with higher doses and alcohol co-ingestion; OR=2.18 (1.52-3.13), dose-related increase in risk; OR=1.19 (0.83-1.70); OR = 4.00 (1.31-12.2); OR=0.93 (0.72-1.21); OR=0.85 (0.55-1.33)	Drivers on benzodiazepines are more likely to be responsible for TAs. OR for benzodiazepines decrease with age. Anxiolytics: alprazolam, bromazepam, diazepam, lorazepam, chlordiazepoxide, clorazepate, oxazepam. Hypnotics: flunitrazepam, flurazepam, loprazolam, lormetazepam, nitrazepam, temazepam.
Longo et al., 2000 Australia [4]	Case-control, April 1995 – August 1996	2500 injured drivers from South Australia	Drivers culpable for TA	Drivers not culpable for TA	Detection of drugs in blood samples	Stratified for different drug concentrations in blood	Benzodiazepines alone: All levels; Subtherapeutic; Therapeutic; Supratherapeutic; Benzodiazepines + alcohol:	OR=2.0 (p <0.05); OR=1.3 (p>0.05); OR=3.3 (p<0.05); OR=3.6 (p<0.05); OR=13.4 (p<0.05)	Confidence intervals for odds ratios are not given. These findings are also presented in Longo et al., 2001 with emphasis on benzodiazepines. The results are similar.

Study	Study design	Source population	Cases	Controls	Exposure assessment	Confounders	Drug	OR (95% CI)	Comments
McGwin et al. 2000 Alabama, US [26]	Case-control, Jan-Dec 1996	39687 residents of Mobile County, Alabama, >= 65y who had a driver 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 Gender Mileage of driving	Benzodiazepines: At-fault drivers, vs. drivers not involved in TA	OR=5.2 (0.9-30.0)	Whether the subjects were on medication during the time accident is not specified.
							At-fault vs. not-at-fault drivers	OR=1.0 (0.2-4.6)	
							Antidepressants: At-fault drivers, vs. drivers not involved in TA	OR=0.8 (0.2-3.0)	
							At-fault vs. not-at-fault drivers	OR=1.3 (0.2 -6.7)	
Mura et al. 2003 France [23]	Case-control	Patients >18y old admitted to emergency departments	900 drivers after traffic accidents	900 patients admitted due to other reasons	Detection of drugs in blood samples	Matched for Age Sex	Benzodiazepines only	OR = 1.7 (1.2 – 2.4)	
Drummer et al., 2004 Australia [33]	Case-control	Drivers killed in TAs in Victoria, New South Wales and Western Australia	Drivers culpable for crashes	Drivers not culpable for crashes	Detection of drugs in blood samples	Age Gender No. of vehicles in crash State Year of crash	Benzodiazepines only	OR=1.27 (0.5-3.3)	Only fatal crashes were analysed. Small sample sizes.
							Opiates only	OR=1.41 (0.7-2.9)	
Movig et al., 2004 The Netherlands [22]	Case-control May 2000 - August 2001.	Injured and non-accident-involved drivers in Tilburg	110 car or van drivers hospitalised after TA	816 drivers randomly selected from moving traffic (stopped for alcohol testing by police)	Positive blood / urine samples	Age Gender Blood alcohol concentration Concomitant drug exposure Season Time of day	Benzodiazepines	OR=5.05 (1.82-14.04)	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
							Opioids	OR=2.35 (0.87-6.32)	
							Drug combinations	OR = 6.1 (2.6–14.1)	
							Drugs + alcohol	OR = 112.2 (14.1-892)	
Dubois et al., 2008 Canada [25]	Case-control, 1993 - 2006	Drivers > 20 years old, involved in fatal TAs between 1993 - 2006	Drivers responsible for TA (as indexed by unsafe driving actions)	Drivers not responsible for TA	Blood sample analysis for benzodiazepines, categorised according to half-life	Age Sex Other medication use Driving history	Short-t ½ (<6h): midazolam 98%	OR=1.02 (0.73 – 1.42)	Drivers positive for alcohol excluded. Age stratified results: higher risk only 25-55 years
							Intermediate t ½ (6-24h): alprazolam 80%	OR=1.53 (1.20 – 1.96)	
							Long half-life (>24h)	OR=1.44 (1.25 – 1.66)	

Table 2: Cohort studies (IRR: Incidence rate ratio, OR: Odds ratio, RR: Relative risk, SIR: Standardised incidence ratio, TA: Traffic accident)

Study, Country	Design, period	Study cohort	Ascertainment of exposure	Ascertainment of non-exposure	Outcome measure, and the way of reporting	Adjustment/ stratification/ controlled variables	Subgroups / different drugs	Results: risk measure (95% CI)	Comments
Ray et al, 1992 Tennessee, US [31]	Cohort, with a case cross-over component for drivers involved in crashes, 1984-1988	16,262 Tennessee Medicaid enrolees aged 65-84y, holding a driving licence	Receiving prescription for a psychoactive drug. Subgroups: Current use, indeterminate use, past use	No prescriptions for benzodiazepines	Injurious crashes reported to Tennessee Department of Safety, Number of crashes per 1000 person-years	Age, sex, race, county of residence, calendar year. Case-crossover study adjusted for alcohol use & driving frequency	Current use of, Any psychoactive Benzodiazepines Cyclic antidepressants Opioid analgesics BDZ + TCA	RR = 1.5 (1.2– 2.9) RR =1.5 (1.1– 2.0), risk increases with dose. RR = 2.2 (1.3 – 3.5), risk increases with dose. RR = 1.1 (0.5 – 2.4) RR = 2.1 (1.1 - 4.2)	
Neutel, 1995 & 1998 Canada [32,37]	Cohort, 1979 - 1986	323,658 individuals > 20y of age included in the Saskatchewan Health Databases	First 2 / 4 weeks following being prescribed a benzodiazepine hypnotic (n=78,070) or an anxiolytic (n=147,726), but not receiving any within 6 months preceding index prescription	Not received a prescription for a benzodiazepines with in 6 months preceding a reference date (n=97,862)	Traffic injury-related hospitalisation following sale of indexed prescription, Number of hospitalisations	Age Sex Other prescribed drugs	All benzodiazepines Hypnotics (triazolam, flurazepam): Within 4 weeks Within 2 weeks Anxiolytics (oxazepam, lorazepam, diazepam): Within 4 weeks Within 2 weeks New users within 4 wks Triazolam Oxazepam Lorazepam Diazepam Flurazepam	OR=3.1 (1.5 – 6.2) OR = 3.9 (1.9 – 8.3) OR = 6.5 (1.9 – 22.4) OR = 2.5 (1.2 – 5.2) OR = 5.6 (1.7 – 18.4) Risk reduces with time since prescription. OR = 3.2 (1.4 – 7.3) OR = 1.0 (0.3 – 3.7) OR = 2.4 (1.0 – 6.3) OR = 3.1 (1.4 – 6.5) OR = 5.1 (2.3 – 11.6)	Benzodiazepine related odds ratios are similar in young (<60y) and elderly (>60y) drivers. However, young age group is an independent risk factor for traffic accidents.
Engeland et al., 2007 Norway [30]	Registry-based cohort Apr 2004 – Sept 2005	All Norwegians aged 18 – 69 years (3.1 million)	Drug dispensing information. Exposed periods: First 7 days / 14 days after dispensing or period corresponding to no. of dispensed defined daily doses	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	Benzodiazepines: Anxiolytics (diazepam, oxazepam, alprazolam) Hypnotics (nitrazepam, flunitrazepam, midazolam) Natural opium alkaloids	SIR = 2.9 (2.5 – 3.5) SIR = 3.3 (2.1 – 4.7) SIR = 2.0 (1.7 – 2.4)	

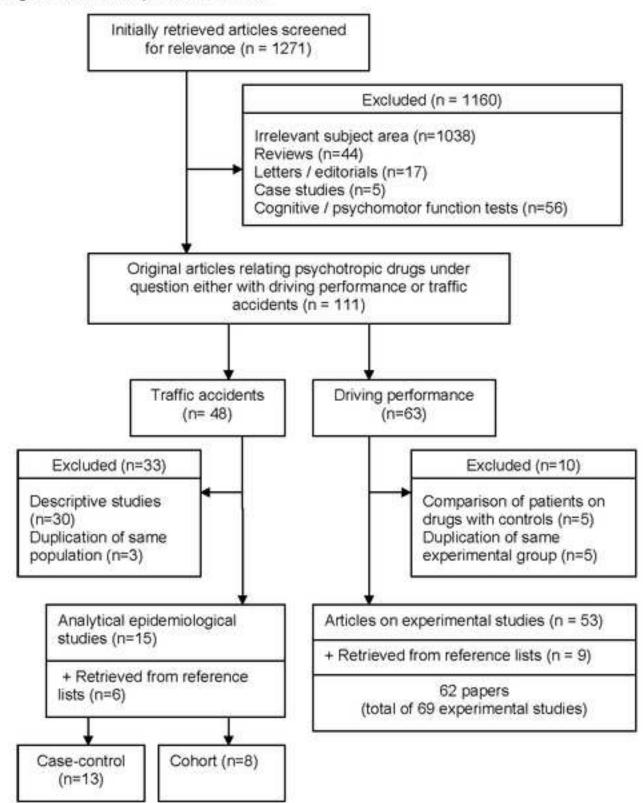| Study	Design	Population	Exposure	Reference period	Outcome	Adjustment	Results	Comments
Bramness et al., 2007 Norway [19]	Registry-based cohort Apr 2004 – Sept 2005	All Norwegians aged 18 – 69 years (3.1 million)	Drug dispensing information. Exposed periods: First 7 days / 14 days after dispensing or period corresponding to no. of dispensed defined daily doses	Period other than the exposed period for the given drug	TA that resulted in a personal injury, Incidence rate	Stratified according to sex, age Adjusted for month	Diazepam: 1st 7 days — SIR = 2.8 (2.2 – 3.2) 1st 14 days — SIR = 2.5 (2.1 – 3.0) 1st 7 days in new users — SIR = 3.3 (1.6 – 5.8)	
Bramness et al., 2008 Norway [38]	Registry-based cohort Jan 2004 – Sept 2006	All Norwegians aged 18 – 69 years (3.1 million)	Drug dispensing information. Exposed period: number of days corresponding to no. of dispensed defined daily doses	Period other than the period defined as exposed period	TA that resulted in a personal injury, Incidence rate	Stratified according to sex, age Adjusted for month	Sedative antidepressants (TCAs, mianserin, mirtazepine) 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., 2008 Norway [18]	Registry-based cohort Jan 2004 – Sept 2006	All Norwegians aged 18 – 69 years (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: 1st 7 days — SIR = 2.3 (2.0 – 2.8) 1st 14 days — SIR = 2.0 (1.7 – 2.2) Zolpidem: 1st 7 days — SIR = 2.2 (1.4 – 3.4) 1st 14 days — SIR = 2.1 (1.5 – 2.9) Nitrazepam: 1st 7 days — SIR = 2.7 (1.8 – 3.9) 1st 14 days — SIR = 2.2 (1.6 – 3.0) Flunitrazepam: 1st 7 days — SIR = 4.0 (2.4 – 6.4) 1st 14 days — SIR = 3.1 (2.0 – 4.6)	The degree of the traffic accident (e.g. injurious, non-casualty) not specified. Risk is higher in young drivers and male drivers.

Gibson et al. 2009 UK [28]	Cohort (self–controlled case series), 1986 - 2004	Individuals 18 – 74y met with MVA and prescribed with sedative drugs during 1986 – 2004. Non-driving participants excluded.	Drug prescription information. Initial exposure: 1st 4 weeks after prescription, Extended exposure: reminder of the course of treatment	Period beyond the time window that spans 4 weeks prior to 1st prescription to 24 weeks after last prescription.	Motor vehicle crash		IRR (99% CI):
							Benzodiazepines (all):
							- 1st 4 weeks — IRR= 1.94 (1.62–2.32)
							- extended use — IRR= 2.38 (2.01–2.81)
							Diazepam – 1st 4weeks — IRR= 1.93 (1.54-2.43)
							  - extended use — IRR= 2.77 (2.20-3.48)
							Temazepam - 1st 4 wks — IRR= 1.56 (1.12-2.17)
							  - extended use — IRR= 1.36 (1.02-1.80)
							Nitrazepam – 1st 4 wks — IRR= 1.66 (0.72-3.86)
							  - extended use — IRR= 1.55 (0.89-2.70)
							Zopiclone – 1st 4wks — IRR= 1.03 (0.68-1.55)
							  - extended use — IRR= 1.40 (1.04-1.87)
							Zolpidem – 1st 4 wks — IRR= 1.04 (0.43-2.48)
							  - extended use — IRR= 1.16 (0.60-2.25)
							Opioids (all)
							- 1st 4 weeks — IRR= 1.70 (1.39 -2.08)
							- extended use — IRR= 1.29 (1.08 -1.54)	

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							Codeine-1st 4 weeks	IRR= 1.61 (1.11 -2.32)
							- extended use	IRR= 1.33 (0.88 -2.00)
							Morphine- 1st weeks	IRR= 1.16 (0.39 -3.45)
							- extended use	IRR= 0.87 (0.43 -1.75)
							Dihydrocodeine	
							–1st 4weeks	IRR= 1.60 (1.14-2.25)
							- extended use	IRR= 1.05 (0.78-1.42)
							Tramadol – 1st 4 weeks	IRR = 1.46 (1.02-2.11)
							- extended use	IRR = 1.34 (1.02-1.76)
							SSRIs (all)	
							- 1st 4 weeks	IRR= 0.92 (0.75 -1.12)
							- extended use	IRR= 1.16 (1.06 -1.28)
							TCAs (all)	
							- 1st 4 weeks	IRR= 0.92 (0.73 -1.16)
							- extended use	IRR= 0.94 (0.77 -1.14)
Bachs et al., 2009 Norway [17]	Registry-based cohort Jan 2004 – Sept 2006	All Norwegians aged 18 – 69 years (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 (coprescription of other impairing drugs excluded)	SIR = 1.3 (1.0 – 1.6)
							Tramadol	SIR = 1.5 (0.9 – 2.3)

Table 3: 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
		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

Figure 1
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Figure 1: Selection process of studies.

Figure 2
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Figure 2

	Accidents / person years		% Weight	
	Exposed group	Non-exposed group		
Ray et al. 1992	46 / 2978	254 / 21578	31.51	1.31 (0.94, 1.80)
Neutel et al. 1995	132 / 37633	23 / 16310	23.31	2.49 (1.59, 4.06)
England et al. 2007	265 / 48769	11193 / 3955769	45.18	1.92 (1.69, 2.17)
Combined (random effects model)				1.81 (1.35, 2.43)

Heterogeneity: Cochran Q = 6.65 (df = 2, p = 0.036), I^2 (Inconsistency) = 70%

Test for overall effect (DerSimonian-Laird): $Z = 3.93$, p<0.0001

Incidence rate ratio (95% confidence interval)

responsible / not-responsible

	Exposed group	Non-exposed group	% Weight		
Lagier et al. 1993	77 / 65	1031 / 841	28.92		0.97 (0.68, 1.38)
Longo et al. 2000	32 / 14	996 / 891	15.94		2.04 (1.05, 4.17)
McGwin et al. 2000	4 / 3	245 / 195	4.04		1.06 (0.18, 7.33)
Drummer et al. 2004	27 / 6	1214 / 376	9.84		1.39 (0.56, 4.16)
Dubois et al. 2008	1122 / 428	42944 / 26882	41.26		1.64 (1.47, 1.84)
Combined (random effects model)					1.41 (1.03, 1.94)

Odds ratio (95% confidence interval)

Heterogeneity: Cochran Q = 9.30 (df = 4, p = 0.054), I^2 (Inconsistency) = 57%

Test for overall effect (DerSimonian-Laird): X^2 = 12.69, p=0.034

Figure 5

Heterogeneity: Cochran Q = 0.33 (df = 2, p = 0.849),
  I^2 (Inconsistency) = 0% (95% CI = 0% to 72.9%)

Test for overall effect (DerSimonian-Laird): X^2 = 48.48, p<0.0001

Supplementary table 1: Benzodiazepines and driving performance: experimental studies (All treatments are single oral doses unless specified otherwise.
BAC: blood alcohol concentration. RT: Reaction time. BRT: Brake reaction time. DDD: defined daily dose. SDLP: Standard deviation of lateral position. SDS: Standard deviation of speed, b.i.d.: twice a daly, t.i.d.: three times a day)

Study [Ref. No.]	a) Experimental design	b) Subjects	c) Treatment conditions: Drug, dose, duration of treatment if >1 dose	d) Timing of test after dosing	e) Task	f) Outcome measures	g) Results	h) Comments/ Considerations
Linnoila and Hakkinen, 1974	Double-blind, placebo-controlled	70 professional drivers (19-22y) In 7 groups (10 each)	No drug or drink (Zero group) Placebo drug & drink Alcohol 0.5g/kg Diazepam 10mg Diazepam 10mg + alcohol Codeine 30mg Codeine 30mg + alcohol	30 minutes	40-minute drive in a driving simulator	Steering wheel reversals, number of times brakes used, number of times clutch used, number of times turning signal used, Speed, BRT, number of neglected instructions, number of collisions, driving off the road	Diazepam: More neglected instructions and collisions Codeine: Less steering wheel reversals and more collisions Diazepam + alcohol: More steering wheel reversals, neglected instructions and collisions Codeine + alcohol: More collisions (All comparisons with the Zero group)	No comparisons with placebo. Any statistical corrections made for multiple comparisons not mentioned, although several different variables were compared.
Moore, 1977	Double-blind, placebo-controlled 2-way crossover	14 males with anxiety required hospital admission. (20-40y)	Medazepam 5–30mg /d (mean 16.5mg) Placebo x 3 weeks	At the end of 3 weeks. Time not specified.	30 min drive in a simulator, Actual driving test	*Driving Simulator:* BRT, speeding, forgetting indications, errors in steering and positioning *Actual driving:* major (dangerous) or minor (technical) driving errors	Increased minor driving errors while on medazepam.	
Hindmarch et al., 1977	Double-blind placebo controlled 2-way crossover	10 volunteers (5 men, 5 women. mean age 27y)	Clobazam 20mg Placebo x 6 nights	morning following 6th dose (day 7)	Multiple car driving manoeuvres	No. of errors and time taken for gap estimation, reverse parking, garage parking. manoeuvring ability	Reverse parking delayed with clobazam. No other changes.	Acute effect not examined. Negative effects on day 7 may be due to absence of drug effect or to tolerance.
Biehl, 1979	Double-blind placebo-controlled 3-way crossover study	24 male students (18-24y) with high neuroticism score	Clobazam 20mg Diazepam 10mg Placebo morning for 3 days	On day 2, timing not specified	Driving in traffic	29 variables of driving performance: Observer-rated items and objective measurements	Break reaction time delayed with diazepam compared to clobazam. No other differences.	Any statistical corrections made for multiple comparisons not mentioned, although several different variables were compared.
Hindmarch and Gudgeon, 1980	Double-blind placebo controlled 3-way crossover study	12 female volunteers (26-40y)	Clobazam 10mg Lorazepam 1mg Placebo t.i.d. x 3 days + 1 dose in morning of 4th day	0.5h after last dose	Multiple car driving manoeuvres	Reverse parking, three point turn, slalom about fixed bollards, width estimation, BRT	Poor performance in parking, three-point turn, slalom and braking after lorazepam compared to clobazam and placebo. No difference in any measures between clobazam and placebo.	

Study	Design	Subjects	Treatment	Test time	Driving task	Measures	Results	Comments
de Gier et al., 1981	Observer-blinded, two-groups	9 patients with anxiety (45.6 ±9.6y) and 13 controls (40.6 ±8.4y) (all men) treated by same physician	Diazepam 5mg – 20mg/d. Duration of treatment not specified	Varying times	Driving in traffic (~ 60km)	Driving performance measured according to a checklist by a trained observer	Poor performance in patients taking diazepam	Temporal relationship between diazepam dosing and testing not specified. Medical conditions of the control group not mentioned.
Betts and Birtle, 1982	Double-blind placebo-controlled 3-way crossover	12 healthy volunteers, all women	Flurazepam 15mg Temazepam 20mg Placebo	12h	Actual driving test	manoeuvring ability, gap-acceptance	Poor manoeuvring skills with flurazepam. More hits on sides in passable gaps after both drugs.	Many drug-unrelated factors may have increased errors: Subjects unfamiliar with vehicle, only 2 minutes of practice. Instructions to drive as fast as possible.
Moskowitz and Smiley, 1982	Double-blind placebo-controlled	48 healthy volunteers (24 men, 24 women, 21-40y) in 3 groups (8 men & 8 women each)	Buspirone 20mg Diazepam 15 mg Placebo daily for 9 days.	Before and 1h after day 1, 8 and 9	Driving simulator task (~ 30 min)	Numerous measures: Lateral position control Speed control Headway control Target (e.g. road sign) detection Emergency decision-making	Day 1, postdose: Worst overall performance with diazepam and best performance with buspirone. Day 8, predose: No significant difference among groups. Day 8, postdose: Worst performance with diazepam and best performance with buspirone.	Diazepam (1.5xDDD) and buspirone (0.67xDDD) doses not comparable. Analyses of extensive number of variables, but no corrections made for multiple comparisons.
O'Hanlon et al., 1982	Double-blind, placebo-controlled, 5-way crossover	9 healthy male driving instructors (24-34y)	Diazepam 10mg Diazepam 5mg Placebo control No-tablet control Early-morning control	1h	Standardised highway driving test (~100km)	SDLP	Increased SDLP after 10mg diazepam than in other conditions.	
Hindmarch and Subhan, 1983	Double-blind, placebo-controlled, 4-way crossover	7 healthy female volunteers (25-40y)	Placebo Midazolam 15mg Alcohol 0.5g/kg Midazolam 15mg + alcohol	10h (i.e. following morning)	Actual driving test	BRT	No impairment with midazolam, alcohol or midazolam alcohol combination.	
O'Hanlon, 1984	Double-blind, placebo-controlled, 4-way crossover	24 former hypnotic drug users, females aged 25-40y	Flurazepam 30mg Flurazepam 15mg Secobarbitone 200mg Placebo 2 nights at 10pm	10-11h & 16-17h after 2nd dose	Standardised highway driving test (~100km)	SDLP	Increased SDLP following all active treatment conditions, both in the following morning (10-11h) and afternoon (16-17h)	
O'Hanlon, 1984	Double-blind, placebo-controlled, 4-way crossover	16 former hypnotic drug users, females aged 25-40y	Loprazolam 2mg Loprazolam 1mg Flunitrazepam 2mg Placebo On 2 nights at 10pm	10-11h & 16-17h following 2nd dose	Standardised highway driving test (~100km)	SDLP	Increased SDLP following all active treatment conditions, both in the following morning (10-11h) and afternoon (16-17h).	Degree of impairment increases with plasma loprazolam concentration

Willumeit et al., 1984a	Double-blind, placebo-controlled, 3-way crossover	12 healthy volunteers (11 men, 1 woman. 21-30y)	Lormetazepam 2mg Flurazepam 30mg Placebo At 10pm daily for 7 days.	Morning after last dose	Driving simulator test (30 min)	Correct tracking executions with steering, Reaction time	Flurazepam: less correct tracking executions and prolonged reaction time compared to placebo Lormetazepam: no difference from placebo	
Willumeit et al., 1984b	Double-blind, placebo-controlled, 8-way crossover	16 healthy volunteers (10 men, 6 women. 20-33y)	Lormetazepam 2mg Diazepam 10mg Mepindolol 10mg Placebo, with out and with alcohol 0.6g/kg.	1h, 3h, 5h	Driving simulator test (30 min)	Correct tracking executions with steering Reaction time	Lormetazepam: impaired correct tracking executions and delayed reaction time, both with and without alcohol. Drug effects potentiated by alcohol Diazepam: impaired correct tracking executions only at 1h postdose. Delayed reaction time throughout. No potentiation of alcohol effects	
Laurell and Tornros, 1986	Double-blind, placebo-controlled, 3-way crossover	18 healthy volunteers, 20-34y	Triazolam 0.25mg Nitrazepam 5mg Placebo at 11pm x 3 nights	9h after 1st & 3rd dose	Simulated driving (~2.5h) Actual driving test (30 min)	*Driving simulator*: BRT *Actual driving*: Number of mistakes in an avoidance manoeuvre	No significant differences except delayed BRT with nitrazepam on day-2 morning.	
O'Hanlon and Volkerts, 1986	Double-blind, placebo-controlled 2-way crossover study	11 insomniacs, women, 26-38y	Placebo 2 days > Temazepam 20mg or Nitrazepam 10mg x 8 days > placebo 3 days (dosing at 10pm)	10h & 16h after day 2, 4, 6, 9, 11, 13 dose	Standardised highway driving test (~100km)	SDLP	Temazepam: Minimum or no impairment at 10h (morning). No impairment in afternoon (16h). Nitrazepam: Significant impairment with repeated doses. Worse in the afternoon.	
Schmidt et al., 1986	Randomised double-blind	32 (20 men, 12 women) outpatients with sleep disorders	Two groups (16 each) Flunitrazepam 2mg Temazepam 20mg 7 nights	Baseline, morning (10h) after day 1 & 7 dose	Standard driving test (25km, ~ 60min)	Steering control	Better performance with temazepam and worse performance with flunitrazepam on both days.	
Brookhuis et al., 1990	Double-blind placebo controlled 3-way crossover	16 patients with insomnia (6 males, 10 females. 26-41y)	Placebo x 2 nights > Lormetazepam 1mg or lormetazepam 2mg or flurazepam 30mg x 8 nights > Placebo x 3 nights	10h & 16h after 2 placebo doses (baseline), 2, 4 & 7 active drug doses and 1 & 3 resumed-placebo doses	Standardised highway driving test (72km)	SDLP Driving speed	Flurazepam: Significant impairment during treatment period. Worse in the morning. Lormetazepam 1mg or 2mg: No impairment during treatment period.	
Friedel et al., 1991	Non-blind study	60 university students (male, 22-26y) in 3 groups (20 each)	Diazepam ~7mg Diazepam ~14mg No drug	Not specified	Standardised driving tasks in a driving simulator	Accuracy of different responses appropriate for each driving scenario	No significant effect of diazepam	Simulation closer to real-life driving. Wide individual variation may be due to complex tasks and perhaps too short practice sessions.

Study	Design	Subjects	Drugs/Doses	Timing	Test	Measures	Results	Comments
Laurell and Tornros, 1991	Double-blind placebo controlled 4-way crossover	24 healthy volunteers (20-32y, moderate drinkers)	Flunitrazepam 2 mg Flurazepam 30 mg Triazolam 0.5 mg Placebo, x 4 nights Alcohol after day 5 testing	9h after 4th dose and then 10 min after alcohol	Drive 20 km in the shortest time in a driving simulator	Average speed Number of crashes	Average speed: More impairment with flurazepam compared to the other two drugs. Additional impairment with alcohol. Crashes: Significant drug effect and alcohol effect. Multiple comparisons not significant.	Covering a distance in shortest possible time, which is not a measure of safe driving, is a demand of the driving task.
Van Laar et al., 1992	Placebo-controlled (Drug treatment double-blind, placebo single-blind)	2 groups of 12 outpatients (6 men, 6 women. 18-50y) with generalised anxiety disorder	Placebo x 7 days > *drug treatment* x 4 weeks > placebo x 7 days *Drug treatment* = Buspirone 5mg t.i.d. x 1wk > 10mg mane, 5mg noon, 5mg nocte x 3wks; or Diazepam 5mg t.i.d. x 4wks	Evening of 7 day of each treatment week, 1.5h after last dose of drug or placebo	Standardised highway driving test (~100km)	SDLP Standard deviation of speed (SDS)	Buspirone: No impairment in SDLP or speed control throughout treatment. Diazepam: Marked increase in SDLP after 1st week, remain significant up to end of 3rd week. Poor speed control after 1 week, normal thereafter.	
Volkerts et al., 1992	Double-blind placebo-controlled 3-way crossover	18 healthy male volunteers, 25-31y	Lormetazepam 1mg Oxazepam 50mg Placebo X 2 nights (10pm)	Simulator: 12h (1st dose). On-the-road: 10h (1st dose), 10h & 16h (2nd dose)	Standardised highway driving test (100km) & Model TS2 driving simulator test	*On-the-road driving*: SDLP *Driving simulator*: Number of correctly executed curve navigation manoeuvres (TC), reaction time	Both drugs increased SDLP (oxazepam > lormetazepam) in the mornings after 1st and 2nd doses. No effects in afternoon following 2nd dose of either drug. Simulated driving: No impairment with any of the drugs. No correlation between performance & plasma drug concentrations.	Oxazepam given as a single dose. Anxiolytic treatment is 30-50mg/d in 3-4 divided doses.
(Kuitunen, 1994)	Double-blind placebo-controlled 6-way crossover	12 healthy volunteers	Diazepam 15 mg Amitriptyline 50mg Mirtazepine 15mg Diazepam + one other drug Placebo	Before, and after 1.5h & 4.5h	Driving simulator test	Tracking errors RT	Increased tracking errors and prolonged RT at both times with amitriptyline and both drug combinations. Tracking error severity higher with drug combinations. Diazepam prolonged Rt after 1.5h. No other significant effects.	
Kuitunen, 1994	Double-blind placebo-controlled 6-way crossover	12 healthy volunteers	Zopiclone 7.5 mg Triazolam 0.25mg Placebo Alcohol 0.8 g/kg Zopiclone / triazolam + alcohol	Before, and after 1,5h & 4.5h	Driving simulator test	Tracking errors RT	Drugs alone and in combination with alcohol increased RT in both times and tracking erros at 1.5h. Triazolam + alcohol increased tracking erros at 4.5h. NO other significant effects.	
Mattila et al., 1994	Double-blind placebo-controlled 5-way crossover	12 healthy volunteers (6 men, 6 women. 19-32y)	Suriclone 0.4 mg Zopiclone 7.5mg Placebo, alone and together with 50 mg chlorpromazine	Before, and after 1.5h, 3.5h & 6h	Driving simulator test	Tracking errors RT	Zopiclone increased tracking errors and prolonged reaction time after 1.5h. No significant effect thereafter. Zopiclone chlorpromazine combination prolonged RT even at 6h postdose.	
O'Hanlon et al., 1995	Double-blind placebo controlled 4-way crossover	16 healthy volunteers (8 men, 8 women, 25-43y)	Ondansetron 1mg b.i.d. Ondansetron 5mg b.i.d. Diazepam 5mg t.i.d. Placebo 1st evening + 7 days	1h after evening dose on day 1 and day 8	Standardised highway driving test (~100km)	SDLP	Increased SDLP with diazepam on both days but not with ondansetron	

Study	Design	Subjects	Drugs/Dose	Timing	Test	Measures	Results	Comments
O'Hanlon, et al., 1995	Double-blind placebo controlled 3-way crossover	18 healthy volunteers (9 men, 9 women, 22-34y)	Lorazepam 0.5mg Suriclone 0.2mg Placebo t.i.d. x 9 days starting from midnight day 1	2-3h after afternoon dose of day 2 & day 9	Standardised highway driving test (~100km)	SDLP Headway maintenance	SDLP: increase with both drugs on both days. Headway maintenance: impairment on both days with lorazepam and day 2 but not day 9 with suriclone	
O'Hanlon, et al., 1995	Randomised double-blind placebo controlled	24 men and 36 women with anxiety (24-64y) in 3 groups	Lorazepam 2mg (n=18) Alpidem 5mg (n=19) Placebo (n=19) b.i.d. run-in, treatment and washout periods, 7, 8 & 6 days respectively	Day 1 before run-in, Day 8 & 15, 3-4h after morning dose	Standardised highway driving test (~100km)	SDLP	Significant increase in SDLP with both drugs on both days 8 and 15. Change is less with alpidem.	SDLP of patients were similar to those of healthy volunteers of the previous two studies
Vermeeren et al., 1995	Double-blind placebo controlled 3-way crossover	17 women (25-51y) with insomnia	Flunitrazepam 2mg Zolpidem 10mg Placebo	10-11h	Standardised highway driving test (~100km)	SDLP	No significant impairment by any of the drugs	
Vermeeren et al., 1998b	Double-blind placebo controlled 4-way crossover	23 healthy women (24-45y)	Chlorpheniramine 8mg / 12mg nocte > terfenadine 60 mg mane Flurazepam 30mg night > placebo morning Placebo mighte & morning X 2 cycles	30min after last morning dose (10h after last nightly dose)	Standardised highway driving test (~100km) Car following test (25km)	SDLP SDS RT speed changes of leading car	Flurazepam: Significant increase of SDLP and SDS with flurazepam compared to other 3 conditions. Significant delay in RT compared to placebo. Chlorpheniramine / terfenadine combinations: No significant impairment.	2 subjects on flurazepam were too drowsy to complete highway driving test
Vermeeren et al., 1998a	Double-blind placebo controlled 7-way crossover	28 healthy volunteers (14 men, 14 women. 23-40y)	Zaleplon 10/20mg >placebo Placebo > zaleplon 10/20mg Zopiclone 7.5mg > placebo Placebo > zopiclone 7.5mg Placebo > placebo Bedtime > 5h later	5h after 2nd dose	Standardised highway driving test (~100km)	SDLP	Zopiclone: Increased after bedtime dosing and after middle of the night dosing. Worse in latter condition. Zaleplon: No significant increase after either bedtime or middle of the night administration of any of the doses.	
(Bocca et al., 1999)	Double-blind, placebo-controlled 3-way crossover	16 healthy volunteers (9 men, 7 women. 20-30y) in 2 groups (9am &11am) of 8.	Zolpidem 10 mg Zopiclone 7.5 mg Flunitrazepam 1 mg placebo single dose at 11pm	10h (9am group) 12h (11am group)	Driving simulator test (~90 min)	Mean variance of lateral position Mean variance of vehicle velocity	Mean variance of lateral position: Increased by zopiclone and flunitrazepam at 10h but not by zolpidem. No effect by any drugs after 12h. Mean variance of vehicle velocity: Not affected by any of the drugs.	Demand was 'to drive as quickly as possible' while maintaining lateral stability. Constant speed was not a direct test demand but was an outcome measure.
Mercier-Guyon et al., 1999	Randomised double-blind 2-way crossover	16 healthy male volunteers (29-44y)	Lorazepam 0.5mg morning, 0.5mg lunchtime, 1mg bedtime Captodiamine 50mg t.i.d. x 7 days	Before and after 7-day treatment. Time not specified	~15-min drive in 900m circuit with different driving manoeuvres	Number of errors due to clumsiness (slalom task), excessive inhibition (braking too early, too conservative gap judging), disinhibition (braking too late, forcing passage when gap is too narrow)	Lorazepam cause more errors due to clumsiness and disinhibition compared to captodiamine. No difference in errors due to excessive inhibition	The disinhibitory effect of lorazepam is noteworthy.

Vanakoski et al., 2000	Double-blind placebo controlled 3-way crossover	9 young (22-24y) and 9 old (55-77y)	Young: Diazepam 15mg, alcohol 0.8g/kg, placebo Old: Diazepam 10mg, alcohol 0.7g.kg, placebo	1.5h before and 4h after	Driving simulator test	BRT, tracking errors (simple and complex), global driving performance	Impaired reaction time and global driving performance in both young and old groups after diazepam. Increased simple tracking errors in both young and old groups in daylight condition.	
Van Laar et al., 2001	Double-blind placebo controlled 3-way crossover	18 healthy male volunteers (25-36y)	Lorazepam 1.5mg Ritanserine 5mg Placebo b.d. X 7 days	3h after last dose	Standardised highway driving test (~100km)	SDLP SDS	Significant increase in SDLP with lorazepam. No effect on SDS by any of the drugs.	Lack of tolerance to lorazepam after 1 week
Verster et al., 2002a	Double-blind placebo controlled 5-way crossover	30 healthy volunteers (15 men, 15 women). Age (SD): 24.0±2.4y	Zaleplon 10mg or 20mg Zolpidem 10mg or 20mg Placebo Middle of the night	4h	Standardised highway driving test (~100km)	SDLP SDS	Zolpidem: SDLP and SDS significantly increased with both doses. Significant dose-response relationship. Zaleplon: No significant difference form placebo.	3 subjects on zolpidem made excessive erros in driving and could not complete the test.
Vermeeren et al., 2002	Double-blind placebo controlled 3-way crossover	30 healthy volunteers (15 men, 15 women 21-45y)	Zopiclone 7.5mg Zaleplon 10mg Placebo	10h	Standardised highway driving test (~100km)	SDLP	Zopiclone: Significantly increased compred to zaleplon and placebo Zaleplon: No difference from placebo	
Iudice et al., 2002	Randomised double-blind placebo-controlled 2-way crossover	12 healthy volunteers (5 men, 7 women. 27-38y)	Lormetazepam 1mg Placebo X 3 nights	Baseline, morning after last dose of each treatment	Simulated drive (~15km) in interacting traffic	Time length of run, number of infractions and speed exceedings, time to collision	No significant differences in any of the measures	
Verster et al., 2002b	Randomised double-blind placebo controlled 2-way crossover	20 healthy volunteers (8 men, 12 women). Age (SD): 25.1±2.0y	Alprazolam 1mg Placebo	1h	Standardised highway driving test (~100km)	SDLP SDS	6 subjects did not complete driving test after alprazolam. Both outcome measures significantly impaired after alprazolam	The SDLP increase equivalent to that caused by alcohol at a blood concentration of 1.5g/l.
Partinen et al., 2003	Randomised double-blind placebo controlled 3-way crossover	18 insomniacs. women (35-60y)	Temazepam 20mg Zolpidem 10mg Placebo Single dose at 2am	Baseline and 5.5h after each dose	Driving simulator test (110km)	Lateral position deviation Speed deviation Reaction time Time to collision	Greater lateral position deviation after zolpidem but not after temazepam. No drug effects on other measures.	
Staner et al., 2005	Randomised double-blind placebo controlled 4-way crossover	23 patients (9 men and 14 women. 18-65y) with primary insomnia	Zolpidem (10 mg) Zopiclone (7.5 mg) Lormetazepam (1 mg) Placebo x 7 nights at 10:30pm	9-11h (7:30am - 9:30am), on day 2 & day 8	Simulated driving in light traffic (~ 60 min)	Lateral position deviation Speed deviation Number of collisions	Zopiclone increased the number of collisions. Lormetazepam increased the speed deviation. No changes by zolpidem.	

Leufkens et al., 2007	Double-blind placebo controlled 3-way crossover	18 healthy volunteers (9 men, 9 women. 20-45y)	Alprazolam slow release (XR) 1mg Alprazolam immediate release (IR) 1mg Placebo	4h	Standardised highway driving test (~100km)	SDLP SDS	SDLP: Increased with both alprazolam preparations. Increase with alprazolam IR is twice the increase caused by alprazolam XR. SDS: No change.	
Boyle et al., 2008	Randomised double-blind placebo-controlled 2-way crossover	32 healthy volunteers (17 men and women. 19–47y)	Eszopiclone 3mg Placebo	Before and 9.00-10.25h after dosing	Closed-circuit driving	BRT	No difference in change BRT from baseline either with placebo or eszopiclone	
Boyle, et al., 2008	Randomised double-blind placebo-controlled 2-way crossover	23 patients with primary insomnia (22 men, 10 women. 20-55y)	Eszopiclone 3mg Placebo	Before and 9.00-10.25h after dosing	Closed-circuit driving	BRT	No difference in change BRT from baseline either with placebo or eszopiclone	
Otmani et al., 2008	Randomised double-blind placebo-controlled 4-way crossover	16 healthy volunteers (12 men and 4 females. 45–55y)	Prolonged-release melatonin 2mg Zolpidem 10mg Both drugs Palcebo	2h & 13h	Driving simulator test (60min, light traffic)	Number of collisions, standard deviation from the speed limit, standard deviation of absolute speed, standard deviation from ideal route	Number of collisions, standard deviation from speed limit and standard deviation from ideal route increased with zolpidem and zolpidem-melatonin combination at 2h. No significant difference at 13h.	
Leufkens et al., 2009	Double-blind placebo-controlled 5-way crossover	25 healthy volunteers (13 men, 12 women. Age (SD): 31.4±7.5y	Gaboxadol 15mg > placebo Zopiclone 7.5mg > placebo Placebo > gaboxadol 15mg Placebo > zolpidem 10mg Placebo > placebo 11pm > 4am	9am (10h after night dose, 5h after early morning dose)	Standardised highway driving test (~100km)	SDLP SDS	Both SDLP and SDS increased after zopiclone 11pm dose, and zolpidem and gaboxadol 4am doses. Only SDS increased after gaboxadol 11pm dose.	
Leufkens and Vermeeren, 2009	Double-blind placebo-controlled 3-way crossover	18 healthy elderly volunteers (10 women, 8 men. 55-75y)	Temazepam 20mg Zopiclone 7.5mg Placebo	10-11h	Standardised highway driving test (~100km)	SDLP SDS	SDLP: Significant increase after zopiclone but not temazepam. SDS: Significantly higher with zopiclone than with temazepam.	
Meskali et al., 2009	Double-blind placebo-controlled 3-way crossover	16 healthy elderly volunteers (8 women, 8 men. 55-65y)	Flunitrazepam 1mg Zolpidem 10mg Zopiclone 7.5mg Placebo 11pm	10h	Driving simulator test (urban route with accident scenarios)	Number of collisions (of 5 accident scenarios per treatment)	No significant increase with any of the drugs.	Total number of collisions among 4 conditions compared with chi-square test.

Supplementary table 2: Antidepressants and driving performance: experimental studies (All treatments are single oral doses unless specified otherwise.
BAC: blood alcohol concentration. RT: Reaction time. BRT: Brake reaction time. DDD: defined daily dose. SDLP: Standard deviation of lateral position. SDS: Standard deviation of speed, b.i.d.: twice a daly, t.i.d.: three times a day)

Study	a) Design	b) Subjects	c) Treatment conditions: Drug, dose, duration if >1 dose	d) Timing of test after dosing	e) Task	f) Outcome measures	g) Results	h) Comments
Landauer et al., 1969	Randomised double-blind placebo-controlled	21 healthy volunteers in 3 groups (6 men, 1 woman in each group) Mean age(SD) :22.1(1.2)y	Amitriptyline 0.8mg /kg night & morning Amitriptyline morning only Placebo > Alcohol after 1st test	2h after morning dose and 15min after alcohol	Driving simulator test	Steering control (Proportion of steering errors to toil correct responses)	Before alcohol: No group differences. After alcohol: no change in double placebo group, but increased in amitriptyline groups. Worst in double amitriptyline group.	Placebo only group did not show any impairment after alcohol despite having a BAC of 0.08% which can impair driving.
Clayton et al., 1977	Randomised double-blind placebo-controlled	40 male volunteers (18-29y) in 4 groups (10 each)	Imipramine 25mg t.i.d. Viloxazine 50mg t.i.d. Placebo t.i.d. x 7 days No drug	Before, 2h after 1st dose, 7 doses (day 3), 21 doses (day 7)	Driving test with a slalom task and a gap estimation task	Number of errors in a weaving task Gap estimation	Weaving task: Imipramine increased the number of errors, when results collapsed across all testing days. No acute effect after a single dose. Gap estimation: No group difference	
Hindmarch et al., 1983	double-blind placebo-controlled 3-way crossover	9 healthy female volunteers (30-45y)	Amitriptyline 50mg Zimeldine 200mg Placebo	Before, 2h & 5h postdose	Brake reaction during actual driving	BRT	2h postdose: Significant impairment only with amitriptyline. 5h postdose: no significant difference between treatments	
O'Hanlon, 1984	Double-blind, placebo-controlled, 5-way crossover	20 healthy male volunteers (22-32y)	Amitriptyline 25mg Doxepin 25mg Mianserin 10mg Oxaprotiline 25mg Placebo t.i.d. x 1day	1:00h-2:15h after last dose	Standardised highway driving test (~100km)	SDLP	Increased SDLP following amitriptyline, doxepin and mianserin. 1/3 of subjects on amitriptyline could not complete the test.	
Hindmarch et al., 1988	Double-blind placebo-controlled 5-way crossover	9 healthy female volunteers (28-55y)	Amitriptyline 50mg Lofepramine 70mg Lofepramine 140mg Nomifensine 100mg Single morning doses	Same day, time not specified	Tracking task in a driving simulator	Mean deviation form target	Increased deviation (poor performance) after amitriptyline. No impairment after other drugs.	
Kuitunen, 1994	Double-blind placebo-controlled 6-way crossover	12 healthy volunteers	15 mg of diazepam 50 mg of amitriptyline 15 mg of mirtazepine Diazepam + one other drug Placebo	Before, and after 1.5h & 4.5h	Driving simulator test	Tracking errors RT	Increased tracking errors and prolonged RT at both times with amitriptyline and both drug combinations. Diazepam prolonged RT after 1.5h. No other significant effects.	

Study	Design	Subjects	Treatments	Testing time	Test	Measures	Results	Comments
Ramaekers et al., 1994	Double-blind placebo controlled 3-way crossover	18 healthy volunteers (9 men, 9 women. 26-54y)	Moclobemide 200 mg b.i.d. Mianserin 10 mg t.i.d. Placebo x 8 days	2.5h after 3rd daily dose on day 1 and day 8.	Standardised highway driving test (~100km)	SDLP	Increased SDLP after mianserin on both days. No change with moclobemide.	
Ramaekers, et al., 1994	Double-blind placebo controlled 4-way crossover	16 healthy volunteers (8 men, 8 women. 23-40y)	Brofaromine 50mg b.i.d. Brofaromine 75mg b.i.d. Doxepin 25 mg t.i.d. Placebo x 8 days	3h after 3rd daily dose on day 1 and day 8	Standardised highway driving test (~100km)	SDLP	Increased SDLP after doxepin on day 1 but not on day 8. No change with brofaromine.	
Ramaekers et al., 1995	Double-blind placebo-controlled 3-way crossover	18 healthy volunteers (10 men, 8 women. 21-45y)	Dothiepin 75mg night x 8days + 150mg night x 13 days Fluoxetine 20mg at night x 22 days Placebo at night x 22 days	14h after 1st, 8th & 22nd dose	Standardised highway driving test (~100km), Car following test	SDLP Headway variability	No significant effects of either drug on SDLP or headway variability	
Robbe and O'Hanlon, 1995	Double –blind placebo-controlled 4-way crossover	16 healthy male volunteers (21-28y)	Paroxetine 20mg morning Paroxetine 40mg morning Amitriptyline 50mg & 25mg morning Placebo X 8 days	1.5h & 5h after morning dose on day 1 & 8	Standardised highway driving test (~100km)	SDLP	Day 1: Impaired with amitriptyline both 1.5h & 5h postdose. No impairment with paroxetine. Day 8: Not impaired by any of the treatments.	
Van Laar et al., 1995	Double-blind placebo controlled 4-way crossover	12 healthy adults (24-38y) & 12 elderly (60-72y). 6 men, 6 women each.	Nefazodone 100mg Nefazodone 200 mg Imipramine 50 mg Placebo b.i.d. x 7 days	2.25h after morning dose on day 1 & day 7	Standardised highway driving test (~100km)	SDLP SDS	Day 1: Imipramine increased SDLP in Adult group but not in Elderly group. No significant effect after nefazodone. Day 7: No significant effect of imipramine on SDLP in either group. SDS: No significant effect by drugs.	Effect of TCA imipramine is in contrast to those observed in epidemiological studies.
Ramaekers et al., 1998	Double-blind placebo controlled 3-way crossover	18 healthy volunteers (9 men, 9 women. 21-35y)	Mirtazapine 15mg x 7days > 30mg x 8days Mianserin 30mg x 7days > 60mg x 8days Placebo x 15days	Morning following the evening dose (15-18h) on day 2, 8, 9, 16	Standardised highway driving test (~100km)	SDLP	Significant, but minor increase in day 2 &16 with mirtazapine. Marginally increased in day 8 with mianserin.	
O'Hanlon et al., 1998	Randomized, double-blind, placebo-controlled, 4-way crossover	37 healthy volunteers (22-40y) enrolled, 22 completed	Venlafaxine 37.5 mg b.i.d. x 14 days Venlafaxine 37.5 mg b.i.d. x 7days > 75 mg b.i.d. x 7 days Mianserin 10 mg t.i.d. x 7days > 20 mg t.i.d. x 7days Placebo t.i.d. x 14 days	2h postdose on day 1, 7, 8 & 15	Standardised highway driving test (~100km)	SDLP SDS	SDLP: Increased after mianserin in all 4 test days. No significant effect with venlafaxine. SDS: Increased after mianserin (compared to placebo) on day 1. No other changes.	7 subjects withdrew due to adverse effects of venlafaxine or mianserin. Results may underestimate the actual effect.
Ridout and Hindmarch, 2001	Double-blind placebo controlled 4-way crossover	16 healthy volunteers (10 men, 6 women. 21-44y)	Tianeptine 12.5 mg Tianeptine 37.5 mg, Mianserin 30 mg Placebo	1.5h, 3h, 4.5h & 6h	Drive on a closed circuit at 30 miles/h	BRT	Mianserin delayed BRT significantly longer than other three conditions. Tianeptine 37.5mg causes a marginal delay. No effect by tianeptine 12.5mg.	

Richet et al., 2004	Double-blind placebo controlled 4-way crossover	12 healthy male volunteers (18-30y)	Milnacipran 50mg Milnacipran 50mg + alcohol Placebo Placebo + alcohol b.i.d. x 1 day	2h	Driving test with reactions to visual and auditory stimuli	BRT Driving performance evaluated by instructors	Impaired with alcohol. Milnacipran has no effect compared to placebo and does not modify the effect of alcohol.	
Wingen et al., 2005	Randomised double-blind placebo-controlled 3-way crossover	18 healthy volunteers (9 men, 9 women. 21-40y)	Escitalopram 10mg x 7 days > 20mg x 8 days Mirtazapine 30mg x 7 days > 45mg x 8 days Placebo x 15 days	10:30am (following the evening dose) on day 2, 9, 16	Standardised highway driving test (~100km)	SDLP SDS	Mirtazapine: Increased SDLP day 2. No effect on day 9 or 16. No effect on SDS. Escitalopram: No effect on either SDLP or SDS.	1 subject could not complete driving test after 30mg single dose mirtazapine
Veldhuijzen et al., 2006	Randomised double-blind placebo-controlled 2-way crossover	7 chronic neuropathic pain patients (4 men, 3 women. 42-58y)	Amitriptyline 25mg Placebo at night x 15 days	13h, on day 2 and day 16	Standardised highway driving test (~100km)	SDLP Subjective self-assessment of driving quality.	Amitriptyline increases SDLP on day 2 but no significant effect on day 16. No difference in subjective assessment of driving quality	SDLP increase by amitriptyline after acute dosing is similar to that caused by BAC of 0.5g/l
Brunnauer et al., 2008	Randomised comparative clinical study	40 depressed patients (18 women, 22 men. 25-57y) + 10 matched healthy controls	Long-term treatment with, Reboxetine (for 20 patients) Mirtazapine (for 20 patients)	Before, 7 & 14 days after initiation of treatment	Driving simulator test	Number of collisions	Before treatment: More collisions in patient groups. Day 14: Significant decline in collisions compared to baseline, with both drugs. Number of collisions similar in patients and healthy controls in day 14.	Timing of dosing before testing is not specified.
Iwamoto et al., 2008a, Iwamoto et al., 2008b	Double-blind placebo controlled 3-way crossover	17 healthy male volunteers (30-42y)	Paroxetine 10mg Amitriptyline 25mg Placebo	Pre-treatment and 1h & 4h postdose	Simulated driving with road tracking, car following and braking	SDLP Variability of headway BRT	1h: No differences between conditions. 4h: Amitriptyline increased SDLP and variability of headway. Paroxetine no effect. No differences in BRT.	Moderate positive correlation between SDLP and plasma amitriptyline concentration.
Shen et al., 2009	Randomised controlled trial	28 patients with major depressive disorder: 14 treated (12 women, 2 men. 29-67y), 14 no treatment (10 women, 4 men. 26-62y)	Mirtazapine 30mg night x 30 days	Morning and afternoon: baseline, day 2, 9, 16 and 30 (untreated group tested baseline, day 2 & 9)	Computerised driving simulator test	Number of crashes, deviation of lateral position	Mirtazapine group: Improvement in road positioning in day 2, 9, 16, 30 compared to baseline. Significant reduction of crashes on day 30 compared to baseline. Untreated: No improvement of driving performance on day 2 or 9. Not tested beyond 9 days. Significant group difference on day 9.	Incomplete follow up of the untreated group.

Supplementary table 3: Opioids and driving performance: experimental studies (All treatments are single oral doses unless specified otherwise. SDLP: Standard deviation of lateral position. SDS: Standard deviation of speed)

Study	a) Design	b) Subjects	c) Treatment conditions: Drug, dose, duration if >1 dose	d) Timing of test after dosing	e) Task	f) Outcome measures	g) Results	h) Comments
Linnoila and Hakkinen, 1974	Double-blind, placebo-controlled	70 professional drivers (19-22y) In 7 groups (10 each)	No drug or drink (Zero group) Placebo drug & drink Alcohol 0.5g/kg Diazepam 10mg Diazepam 10mg + alcohol Codeine 30mg Codeine 30mg + alcohol	30 minutes	40-minute drive in a driving simulator	Steering wheel reversals, number of times brakes used, number of times clutch used, number of times turning signal used, Speed, brake reaction times, number of neglected instructions, number of collisions, driving off the road	Diazepam: More neglected instructions and collisions Codeine: Less steering wheel reversals and more collisions Diazepam + alcohol: More steering wheel reversals, neglected instructions and collisions Codeine + alcohol: More collisions (All comparisons with the Zero group)	No comparisons with placebo. Any statistical corrections made for multiple comparisons not mentioned, although several different variables were compared.
Menefee et al., 2004	Prospective one group pre-test, post-test design	23 patients (17 men, 6 women. 18-67y) on <15mg equivalent of oxycodone	Transdermal fentanyl 1month titration period and 1 month stabilization period (median 50micrograms/h) period	Not applicable	Driving simulator task	Reaction time and errors in braking, steering, speed and signalling	No differences in outcome measures before and during treatment.	
Verster et al., 2006	Randomised double-blind placebo-controlled 5-way crossover	18 healthy volunteers (6 men, 12 women). Mean (SD) age : 24.0 (1.6)y	Oxycodone / Paracetamol 5/325mg, 10/650mg Bromofenac 25mg, 50mg Placebo	1h	Standardised highway driving test (~100km)	SDLP SDS	No difference between active drugs and placebo conditions in any of the measures. Significant dose-response relationship for oxycodone / paracetamol	

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