Driving Under the Influence of Non-Alcohol Drugs — An Update Part I: Epidemiological Studies

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ABSTRACT: Epidemiological studies of the association between drug use and involvement in road traffic crashes (RTCs) published from January 1998 to February 2015 have been reviewed. Cohort and population studies compared RTC involvement among drug users and non–drug users, case-control studies compared drug use among RTC-involved and non–RTC-involved drivers, and responsibility studies and case-crossover studies were performed for RTC-involved drivers. Difficulties associated with the types of studies are discussed with a special focus on case-control studies. Statistically significant associations between drug use and RTC involvement were found for benzodiazepines and z-hypnotics in 25 out of 28 studies, for cannabis in 23 out of 36 studies, for opioids in 17 out of 25 studies, for amphetamines in 8 out of 10 studies, for cocaine in 5 out of 9 studies, and for antidepressants in 9 out of 13 studies. It was a general trend among studies that did not report significant associations between the use of these drugs and increased RTC risk that they often had either poor statistical power or poor study design compared to studies that found an association. Simultaneous use of two or more psychoactive drugs was associated with higher RTC risk. Studies on the combination of alcohol and drugs have not been reviewed in this article even though this combination is known to be associated with the highest RTC risk.

KEYWORDS: Amphetamines, antidepressants, benzodiazepines, cannabis, cocaine, drugged driving, DUID, epidemiology, hypnotics, opioids, road traffic crashes (RTCs).

INTRODUCTION

A review article on the effect of drug use on road traffic safety was published in this journal in 2000 [90]. The article included experimental and epidemiological studies published before 1998 for the following drug groups: benzodiazepines and related drugs, cannabis, opioids, amphetamine and related drugs, antihistamines, and antidepressants. Many investigations have been performed since then. In this article, epidemiological studies on drugs and traffic safety published after 1998 are reviewed. An update of experimental studies will be published in a forthcoming issue of this journal together with a summary of the combined knowledge from epidemiological and experimental studies.

Experimental studies can be used to determine whether a drug may impair driving-related functions and are most commonly performed for medicinal drugs using healthy individuals taking relatively small drug doses. In many countries it is impossible to perform experimental studies of illicit drugs in humans for ethical reasons. In countries where such studies are allowed, the doses given and drug exposure times are often lower than those used by problematic drug users and may therefore not reflect the actual risks in road traffic.

The resulting effects of drug use on traffic safety are a function of the degree to which the drugs are used, the levels and manners in which they are used, and the populations that are using them [86]. Therefore, epidemiological studies are needed to determine the actual consequences of drug use on road traffic safety.

An important advantage with epidemiological studies is that they may be used to determine the impact of drug use in the general population of drivers, which includes users of illicit drugs, patients taking medicinal drugs for treatment of illness or relief from symptoms, and drivers using the same type of drugs for recreational purposes or because of drug addiction. In the latter case, the taken dose may be substantially higher than doses taken by patients for therapeutic purposes. Medicinal drugs that are used for the treatment of severe pain, anxiety, insomnia, narcolepsy, or hyperactivity are among those most frequently used for nontherapeutic purposes.

This review is primarily based on articles found by searching the major scientific literature databases. We have only included studies published in English.

I. METHODOLOGICAL ISSUES

A. Challenges and Difficulties

There are four main types of epidemiological studies on the incidence and consequences of drug-impaired driving in various driving populations, primarily those involved in road traffic crashes (RTCs): (a) cross-sectional, descriptive studies on the prevalence of drug use; (b) cohort and population studies on RTC involvement among drug users compared to non–drug users; (c) case-control studies

comparing drug use among RTC-involved and non–RTC-involved drivers; and (d) studies on RTC-involved drivers only, such as responsibility studies and case-crossover studies. Results from cross-sectional studies may be used to propose hypotheses on RTC risk related to the use of individual medicinal or illicit drugs, whereas cohort studies, case-control studies, responsibility studies, and case-crossover studies are analytical studies that may be used to estimate the actual RTC risks associated with the use of individual drugs.

A general difficulty in all types of epidemiological studies of RTCs is a possible selection bias in the inclusion of RTC-involved drivers. It is only possible to include drivers involved in RTCs that are recorded in databases or registries, self-reported RTC-involved drivers, injured drivers receiving treatment, drivers involved in RTCs that are subject to blood sampling for toxicological testing, or fatally injured drivers subject to legal autopsy. If including a control population, a selection bias may occur as well.

Knowledge about alcohol and drug use may be incomplete for both those involved in accidents and for a control population of drivers who are not crash-involved. If data is based on self-reports, underreporting might be a significant problem [1,37,54,89,113]. If basing the study on drug testing of biological samples, only cases where sampling is performed are included, and a limited number of psychoactive substances are looked for in most studies. Thus, the use of some drugs or drug combinations that can affect the results may not be detected.

If information is obtained from prescription registries, the data just tells us that the medicinal drug has been dispensed at a pharmacy, not that it is actually taken and if so, taken in recommended doses. Another difficulty is related to the fact that the patient has received the prescription for a medicinal drug due to illness or disease, which itself may affect the RTC risk. In fact, the patient might be a more dangerous driver in some cases of nonmedicated disease than when medication is taken. In studies using data from prescription registries, the use of alcohol and illicit drugs is not taken into consideration, as well as nonrecorded use of medicinal drugs.

RTC involvement does not mean responsibility. In RTCs between a drug-impaired driver and a sober driver, the driver who is injured and therefore included in the study as RTC-involved might not be the one who was responsible for the RTC. This will cause a "dilution" of the calculated RTC risk, as previously described for alcohol in case-control studies [45]. Studies of only responsible drivers would eliminate this error. In some studies, drivers injured or killed in single-vehicle RTCs are investigated separately because they are almost always responsible in such cases.

A low participation rate may give a significant sampling bias. The refusal rate may be related to study design and/or to cultural issues. It might be suggested that a large proportion of those who voluntarily participate in studies are conscientious individuals without significant social or behavioral problems, whereas some of those who refuse to participate might be careless or might not want to reveal any less acceptable behavior.

Covariates (confounding or interacting variables) that are usually included in matching cases and controls or in data analysis are: age, gender, time of day/week, and geographical region. Some other possibly important covariates are: driving experience, personality characteristics, state of physical and mental health, sleep deprivation, state of alertness, exhaustion, distractions, use of caffeine, hunger, thirst, socioeconomic factors, driving alone or with passengers, speed limit, weather conditions, visibility, traffic density, the condition of the road, and the condition of the motor vehicle.

Covariates related to personality are often not included. If cases and controls are different in relation to impulsivity, sensation-seeking and risk-taking behavior, the calculated risk for RTC involvement will not reflect the risk posed by the drug alone, but a combination of substance use with personality factors. A particular problem is the association between the use of illicit drugs and risk-taking personality [10,14,33,65,119], which in itself may be associated with high RTC risk also in the absence of drug use. In addition, risk-taking behavior might again be increased after using some types of drugs.

It is often difficult to relate any increased RTC risk to drug doses or blood drug concentrations in epidemiological studies due to lack of statistical power; therefore, assessments are in most studies performed using dichotomous data (drug used: yes/no).

It is important to remember that epidemiological studies cannot be used to prove causality; the studies can merely be used to document an association between drug use and involvement in RTCs. Any observed association may also, at least partly, be related to confounding factors that are not controlled for.

Guidelines for research on drugged driving were published in 2008 [118]. They include recommendations for roadside surveys, studies of drivers injured in RTCs (hospital studies), fatal RTC studies, and the collection and analysis of biological samples. Similar recommendations for cohort studies or research using registries or self-reported data have, to our knowledge, not been published. However, general guidelines on observational studies in epidemiology have been developed [116].

More challenges and difficulties that are specific for different study types are discussed in sections C-E.

B. Cross-Sectional Studies

The use of drugs by drivers who are involved in RTCs is investigated in descriptive cross-sectional studies. After alcohol, the most frequently found drugs are cannabis, benzodiazepines, stimulants, and opioids [30,51,72,73,91,105]. Combinations of alcohol and drugs or multiple drugs are also commonly found. We have not reviewed cross-sectional studies in this article.

C. Cohort and Population Studies

RTC involvement among drivers who are using a specified drug may be compared with RTC involvement among drivers who are not using the drug. The use of medicinal drugs can be studied by using data from prescription registries, and data on RTC involvement or injury may be obtained from accident registries or health databases. The date for dispensing from a pharmacy is regarded as the starting date for drug use. RTCs during the first 7 or 14 days after dispensing date are often measured and compared with RTCs among drivers who have not purchased the same type of drug. The drug-using driver may be his own control; the number of RTCs during periods of drug use is then compared with RTCs during periods without using the drug in question. This type of study is called "case-crossover study" and is discussed in section E.

The selection of the drivers in the drug-exposed and non–drug-exposed cohorts is independent of any RTC involvement; this is in contrast to case-control studies, where RTC-involved drivers are selected as cases, as well as in responsibility studies, where only RTC-involved drivers are studied.

Studies of the association between self-reported use of medication or illicit drugs and RTCs are also performed. In those surveys, participants are selected by random within geographical areas and sometimes within specified age groups by using population registries of different types, such as driver license, health, social insurance, or resident registries. Information is gathered by using questionnaires or telephone interviews. The frequency of drug use is recorded as well as involvements in RTCs under the influence of the drug in question and RTCs when not using the substance in question. A list of cohort and population studies published after 1998 is presented in **Table 1**.

D. Case-Control Studies

Case-control studies are in general used to study the association between a defined exposure and an outcome of active exposure and are sometimes regarded as the optimal methodological approach for studying the RTC risk when driving after using alcohol or drugs [11,62]. This statement might be questionable due to a number of difficulties, which we have discussed quite extensively below. However, there is no doubt that a well-performed case-control study of drug use and RTC involvement provides important information on the association between drugs and RTC risks among drivers in actual road traffic.

Cases are drivers involved in RTCs. They may be selected from police records, insurance records, hospital records, postmortem autopsy records, other databases or registries on RTC-involved drivers, or by self-reported RTC involvement.

Controls are drivers who are not involved in RTCs and may be selected from random traffic, from driver's-license databases, or by self-reported noninvolvement in RTCs.

The exposure to drugs may be determined in different ways: by analyzing drugs in biological samples (blood, oral fluid, urine, or sweat), by self-reporting, or by using data from prescription registries.

If using biological samples, blood or oral fluid may be used to study real-time drug exposure (i.e., at the time of sample collection), whereas samples of sweat or urine may be used to detect drug use once or more during the last days or weeks, to study drug-using drivers (i.e., not only drug exposure at the time of sample collection).

Normally, the odds ratios (ORs) for involvement in RTCs are calculated in case-control studies using logistic regression analysis. The reference group in the regression analysis may either be (a) drivers who have not used alcohol or any psychoactive drugs before driving; or (b) drivers who have not used the substance in question (but they may have used alcohol or other drugs). Those two calculation options give different ORs.

Most often the OR is calculated for single drug use (i.e., not combined with alcohol or other drugs), but sometimes the OR is calculated for any use of that particular drug (either alone or in combination with alcohol or drugs). Previous studies have shown that those calculation methods may give very different ORs [46,48]. The chosen method is in some studies not properly described.

An important requirement for case-control studies is that cases and controls must be selected by random from the same population; i.e., controls should be selected in an unbiased manner from those individuals who would have been included in the case series, had they been involved in an RTC [85]. To enable this, cases and controls should be matched regarding important covariates, or more commonly, covariates should be included in the data analysis. It is very difficult to control for all significant factors. Therefore, the outcome of case-control studies

Table 1. Cohort and population studies of road traffic crash (RTC) involvement among drug users and non-drug users

Authors, year country, ref.	Methodology	Population size, survey, or cohort	Data source[a]	Substances assessed[b]	Covariates[c]
Asbridge et al. 2005, Canada [3]	Student survey	6,087 senior students	Questionnaire or interview	can[d]	edu, exp, fak, sex urb
Bachs et al., 2009 Norway [5]	Population study	3.1 million age 18–70	Prescription and RTC DB	cod[d], tra	age, sex
Bramness et al. 2007, Norway [20]	Population study	3.1 million age 18–69	Prescription and RTC DB	car[d], dia[d] sal	—
Bramness et al. 2008, Norway [22]	Population study	3.1 million age 18–70	Prescription and RTC DB	and[d]	—
Bramness et al. 2009, Norway [21]	Population study	3.1 million age 18–70	Prescription and RTC DB	lit, val	age, sex
Bramness et al. 2012, Norway [19]	Population study	3.1 million age 18–70	Prescription and RTC DB	met[e]	age, sex
Engeland et al. 2007, Norway [35]	Population study	3.1 million age 18–69	Prescription and RTC DB	ben[d], bet cra, nsa[d] opi[d], pen[e]	age, sea, sex
Fergusson & Horwood 2001, New Zealand [38]	Birth cohort study	907, age 18–21	Questionnaire or interview	can[d]	age, att, beh, ddb exp, sex
Fergusson et al., 2008 New Zealand [39]	Birth cohort study	936, age 18–21	Questionnaire or interview	can	beh, dui, exp
Gerberich et al., 2003 US [43]	Healthcare cohort study	64,657	Questionnaire or interview	can[e]	age, bmi, dis, dri edu, eth, mar, smo
Gustavsen et al. 2008, Norway [52]	Population study	3.1 million age 18–69	Prescription and RTC DB	hyp[d]	age, sex
Lai et al., 2014 Taiwan [69]	Exposed and non-exposed cohorts	Exposed: 8,188 non-exp.: 32,752	Health insurance DB	zol[d]	age, dis, dru, sex
Mann et al., 2007 Canada [79]	Population survey	2,676	Questionnaire or interview	can[d]	age, edu, inc, mar sex
Mann et al., 2010 Canada [80]	Population survey	8,481	Questionnaire or interview	can[d]	age, dri, edu, exp inc, mar, sex
Neutel, 1998 Canada [92]	Population study	1 million	Prescription, health insurance and hospital DB	ben[d]	age, alc, dru, sex
Pulido et al., 2011 Spain [99]	Population survey	17,484	Questionnaire or interview	can[d], coc[d]	age, alc, dru, edu eth, occ, exp, sex
Skurtveit et al., 2012 Norway [110]	Population study	3.1 million age 18–69	Prescription and RTC DB	adb[e]	age, sex
Stoduto et al., 2012 Canada [112]	Population survey	8,107	Questionnaire or interview	coc[d]	age, dui, exp, inc sex
Wadsworth et al. 2006, UK [117]	Population survey	4,754	Questionnaire or interview	can[d]	age, dis, dri, edu inc, occ, per, sex smo

[a] Abbreviations for data sources: DB = database or registry.
[b] Abbreviations for substances: adb = antidiabetics; and = antidepressants; ben = benzodiazepines; bet = beta blockers; can = cannabis; car = carisoprodol; coc = cocaine; cod = codeine; cra = calcium receptor antagonists; dia = diazepam; hyp = hypnotics; lit = litium; met = methadone; nsa = non-steroidal anti-inflammatory drugs; opi = opioids; pen = pencillins; sal = salbutamol; tra = tramadol; val = valproate; zol = zolpidem.
[c] Abbreviations for covariates: age = age of driver; alc = alcohol used; att = attitudes to risky driving; beh = driving behavior; bmi = body mass index; ddb = drink driving behavior; dis = disease or health status; dri = drinking habits; dui = previous driving under the influence; dru = drug(s) used; edu = education grade; eth = ethnicity; exp = driver experience or milage; fak = used fake ID to get alcohol; inc = income; mar = marital status; occ = occupational status; per = personality; sea = season of the year; smo = smoking; urb: urbanity.
[d] Statistically significant association between drug use and RTC was reported.
[e] Statistically significant association was reported for some groups of drivers.

seldom determines the increase in RTC risk due to only the drug *per se*, but instead the RTC risk posed by the drug user, which also includes behavioral and personality factors in addition to physical and mental health. Long-term drug abuse may also cause somatic and mental changes that may increase the RTC risk. Case-crossover studies (see section E) may be used to overcome this problem, at least partly, because important covariates such as age, gender, and behavioral and personality factors are the same.

If using biological samples, blood samples should ideally be collected from both cases and controls because blood samples reflect recent intake and exposure to drugs. Blood samples should be taken from cases immediately after RTCs to eliminate concentration changes due to metabolism or postmortem redistribution [40,53,104]. Blood samples are the best type of biological matrix for drug analysis that can be used for evaluation of RTC risk related to the drug concentration, which is expected to reflect the drug concentration in the central nervous system and therefore most likely the degree of drug influence.

The controls are drivers who are not involved in RTCs and who have the option of refusing to participate. Some drivers may refuse because of fear of detection and prosecution, whereas others may refuse because of the invasiveness or intrusiveness of the sampling or because they do not want to spend the amount of time required. The refusal rate is often particularly high when collecting blood samples; in recent roadside surveys of alcohol, drugs, and driving, the refusal rate was 24% in Lithuania; it was 52% when collecting blood or oral fluid in Belgium, and 25% refused to give a blood sample but 20% were willing to give a sample of oral fluid instead of blood in the Netherlands [60]. In American roadside surveys, 50–60% refused to give blood samples [67,68].

Oral fluid has sometimes been collected from controls in case-control studies because it reflects drug presence in blood [109,115]. When collecting oral fluid, the refusal rate was less than 10% in roadside surveys in Denmark, Norway, Poland, Portugal, and Spain; however, it was higher in Sweden, Finland, the Czech Republic, and Hungary [60]. The refusal rates were about 20–30% in North American roadside surveys [8,64,68]. It has thus been possible to obtain high participation rates if collecting oral fluid when using a good study design. However, other factors, such as cultural issues, may also have affected the participation rate.

Because of different drug concentration in oral fluid and blood, it can be difficult to compare the prevalence of drugs. However, the prevalence of a drug in paired samples of oral fluid and blood from the same cohort are equal if using equivalent (not equal) cutoff concentrations [47,49], then the average drug detection time in oral fluid will be the same as in blood. Equivalent cutoff concentrations for oral fluid and blood have been used in a few previous studies [12,46,48,57]. If equivalent cutoff concentrations are not used, the OR for RTC involvement will either be overestimated or underestimated, depending on differences in drug detection times in oral fluid and blood after intake of a single drug dose. Drug concentrations in oral fluid cannot be used to accurately estimate concentrations in blood because of large inter- and intraindividual variations in drug-concentration ratios between oral fluid and blood [70,120].

Some studies have compared results for blood samples from cases with urine samples from controls or used a mixture of data from blood and urine samples [34,87,121]. That type of case-control design makes interpretation of results difficult, because a drug finding in urine does not indicate active drug exposure while driving. Urine samples may be positive for a drug and/or metabolites for a number of days longer than a blood sample, with very large variation between individuals, and it is therefore impossible to define equivalent cutoff concentrations in blood and urine, and the calculated OR for RTC involvement may be very much underestimated. If using urine samples, urine should be collected from all cases and all controls. This type of study will determine any association between drug users and RTCs and not between active drug exposure and RTCs.

Biological samples should be analyzed for a broad range of psychoactive substances. Multidrug use and combinations of alcohol and drugs is commonly observed among drivers injured or killed in RTCs [72,73,105] because it may increase impairment and thus also the RTC risk. If only analyzing for a small number of substances, multidrug use may not be detected and the calculated ORs may be incorrectly high, while risks related to drugs that are not analyzed will not be detected at all.

Some studies have compared results for blood samples from cases with self-reported drug use among controls [15,55]. It is well known that underreporting of drug use is common and it may vary for different drugs and between different cohorts or cultures [1,37,54,89,113]. However, results of studies of this type may be used to propose hypotheses on increased RTC risk after using certain drugs.

Houwing et al. recently discussed several random and systematic errors that may occur in case-control studies, such as sample size, low cell counts, geographical bias, sampling method, inclusion criteria, refusals, distributions of age and gender, time lapse between accident or apprehension and sample collection, analytical methods, and confounding factors [61].

It is practically impossible to fulfill the requirements for optimal case-control studies of drugs and RTCs. It is easy to handle some confounding factors, such as age, gender, time of day, day of week, and type of road or crash site, but more difficult to handle selection bias, low participation rate, and lack of control of important confounding factors. The calculated OR for involvement in an RTC will not only be related to risks posed by the substance *per se*, but very much affected by the study design, participation rate, confounding factors that are not adjusted for during matching or data analysis, and often an uncertainty introduced because of using different biological fluids from cases and controls. Lists of case-control studies published in English after 1998 are presented in **Tables 2** and **3**.

Table 2. Case-control studies using biological samples (cases were killed or injured in RTCs, controls were not involved in RTCs)

Authors, year country, ref.	Cases	Participation rate (%)[a]	Controls	Participation rate (%)[a]	Samples[b]	Cutoffs[c]	Substances analyzed[d]	Substances assessed[d]	Covariates[e]
Assum et al. 2005, Norway [4]	87 killed or injured car/van/ minibus drivers	Unk.	410 drivers in normal traffic	87	Alcohol: B or BR Drugs: B (cases) OF (controls)	No	alc, amp, ben, can coc, ecs, opi	amp[f], ben[f], can mul[f], opi	
Beirness et al. 2013, Canada [9]	902 fatally injured drivers	Unk.	4,711 drivers in normal traffic	68.4	Alcohol: B or BR Drugs: B (cases) OF (controls)	No	alc, amp, ben, can opi	can[f]	
Bogstrand et al. 2012, Norway [17]	96 injured car/ van drivers	93	5,305 drivers in normal traffic	93.8	Cases: B Controls: OF	Yes	alc, amp, ben, can coc, ecs, opi, zhy	mul[f]	age, sex tim
Bogstrand & Gjerde 2014, Norway [16]	2,738 drivers arrested for DUI (BAC <0.2 g/L) (794 RTC-involved)	Unk.	9,375 drivers in normal traffic with BAC <0.2 g/L	94	Cases: B Controls: OF	Yes	alc, amp, ben, can coc, ecs, opi, zhy	amp[g], ben[g], can[g] coc[g], ecs[g], mul[g] opi[g], zop[g]	age, geo sea, sex tim
Brault et al., 2004 Canada [23]	512 killed drivers passenger cars	38.3	5,931 drivers in normal traffic	49.6	Alcohol: B or BR Drugs: U	Yes	alc, amp, bar, ben can, coc, opi, pcp opi, pcp	amp[f], bar, ben[f] can[f], coc[f], opi[f] pcp[f]	age, sex tim
Compton & Berning 2015, US [25]	3,095 drivers involved in RTC	79.6	6,190 drivers in normal traffic	83.7	OF	Yes	alc, and, can, opi sed, sti	and, can[f], opi sed[f], sti	age, geo sea, sex tim
Gjerde et al., 2011 Norway [48]	204 killed car/ van drivers	61	10,540 drivers in normal traffic	88	Cases: B Controls: OF	Yes	alc, amp, ben, can car, coc, ecs, opi zhy	amp[f], ben, can can, mul[f], zop	age, sea sex, tim
Gjerde et al., 2013 Norway [46]	508 killed car/ van drivers	61	9,210 drivers in normal traffic	94	Cases: B Controls: OF	Yes	alc, amp, ben, can coc, ecs, opi, zhy	amp[f], ben[f], can mul[f], zop	age, geo sea, sex tim, urb
Hels et al., 2011 [56] Bernhoft et al. 2012 [12] Europe (4 countries)	1,112 killed car/van drivers	FI 94.3 NO 59 PT 79 SE 94	21,917 drivers in normal traffic	FI 52 NO 94 PT 97 SE 62	Alcohol: B or BR Drugs: B (cases) OF (controls)	Yes	alc, amp, ben, can coc, ecs, opi, zhy	amp[f], ben/ zhy[f] can, coc[f], mul[f] opi[f]	age, geo sex
Hels et al., 2011 [56] Hels et al., 2013 [57] Bernhoft et al., 2012 [12] Europe (6 countries)	2,490 injured car/van drivers	BE 94.6 DK 95 FI 91.5 IT 100 LT 100 NL unk.	15,832 drivers in normal traffic	BE 48 DK 95 FI 52 IT 100 LT 76 NL 95	Alcohol: B or BR Drugs: B (cases) B or OF (controls)	Yes	alc, amp, ben, can coc, ecs, opi, zhy	amp[f], ben/zhy[f] can[f], coc, mul[f] opi[f]	age, geo sex
Hou et al., 2012 Taiwan [59]	254 injured drivers	93	254	76	Alcohol: B or BR Drugs: B or U	No	alc, amp, and, bar ben, can, coc, opi pcp	and, bar, ben[f]	age, geo mar, sex tim
Kuypers et al., 2012 Belgium [66]	337 injured car/van drivers	27.0	2,726 drivers in normal traffic	44.8	Alcohol: BR Drugs: B	Yes	alc, amp, ben, can coc, ecs, opi, zhy	amp[f], ben, can[f] coc, mul[f], opi zhy[f]	age, sex tim
Li et al., 2013 US [74]	737 killed drivers	35.6	7,719 drivers in normal traffic	70.7	Alcohol: B or BR Drugs: B or U (cases) OF (controls)	No	alc, amp, and, anh ben, can, car, coc ecs, ket, opi, pcp zhy	can[f], opi[f], mul[f] sti[f]	age, geo sex, tim
Marquet et al., 1998 France [81]	296 age 18–35 injured drivers	Unk.	278 age 18–35 other patients	Unk.	Cases: U Controls: U	Yes	amp, can, coc, ecs opi	can[h], opi	age, geo sex

Table 2. (Continued)

Authors, year country, ref.	Cases	Participation rate (%)[a]	Controls	Participation rate (%)[a]	Samples[b]	Cutoffs[c]	Substances analyzed[d]	Substances assessed[d]	Covariates[e]
Mathijssen & Houwing 2005, Netherlands [82]	184 injured drivers	88.9	3,374 drivers in normal traffic	87.6	Alcohol: B or BR Drugs: B (cases) B, U or Q (controls)	No	alc, amp, and ben, can, coc opi	ben[f], can cod, mor[f] mul[f]	
Movig et al., 2004 Netherlands [87]	110 injured drivers	Unk.	816 drivers in normal traffic	79.3	Alcohol: B or BR Drugs: B or U	No	alc, amp, and bar, ben, opi	amp, ben[f] can, coc mul[f], opi	age, sea sex, tim
Mura et al., 2003 France [88]	900 injured drivers	96	900 non–trauma patients	96	B and either U or SW	Yes	alc, amp, and bar, ben, can coc, opi	ben[f], can[f] mor[f]	age, sex
Perttula et al., 2014 Finland [97]	427 killed drivers	Unk.	687 drivers at petrol station	63.4	Cases: B Controls: B, Q	Yes	anh	anh	age
Romano et al., 2014 US [106]	1,766 killed drivers	Unk.	3,424 drivers in normal traffic	71	Alcohol: B or BR Drugs: B or U (cases) OF (controls)	No	alc, amp, and anh, ben, can car, coc, ecs ket, opi, pcp zhy	can[f], opi sti[f]	age, eth sex
Woratanarat et al., 2009 Thailand [121]	200 injured drivers	Unk.	849 drivers at petrol station	Unk.	Alcohol: B or BR Drug: U, Q	Yes	alc, amp, and ane, anh, bar ben, can, coc mit, mus, opi	amp[f], and anh, can mor[f], mul	

[a] Abbreviations for countries: FI = Finland; NO = Norway; PT = Portugal; SE = Sweden; BE = Belgium; DK = Denmark; IT = Italy; LT = Lithuania; NL = The Netherlands.
[b] Abbreviations for samples: B = blood; BR = breath; OF = oral fluid; Q = questionnaire or interview; SW = sweat; U = urine.
[c] Equivalent cutoff for samples and controls.
[d] Abbreviations for substances: alc = alcohol; amp = amphetamines; and = antidepressants; ane = antiepileptics; anh = antihistamines; bar = barbiturates; ben = benzodiazepines; can = cannabinoids; car = carisoprodol; cod = codeine; coc = cocaine/metabolites; ecs = ecstacy (MDMA); ket = ketamine; mit = mitragynine; mor = morphine/heroin; mul = multiple drug use; mus = muscle relaxants; opi = opioids; sed = sedatives; sti = stimulants; zhy = z-hypnotics (zolpidem, zopiclone); zop = zopiclone.
[e] Abbreviations for covariates: age = age of driver; eth = ethnicity; geo = geographical area; mar = marital status; sea = season of the year; tim = time of day or week; urb = urbanity.
[f] Statistically significant association between drug use and RTC was reported.
[g] Calculated ORs were not relative to sober drivers; ranks between ORs for arrest after using single or multiple drugs were calculated.
[h] Statistically significant association was reported for some groups of drivers.

E. Responsibility and Case-Crossover Studies

Responsibility studies are case-case studies performed without any non-RTC control group. Judgments about responsibility for causing the RTC are made by examining the circumstances leading up to the RTC without having information about alcohol or drug use by the drivers, who are classified according to their degree of responsibility for the RTC. Then drug use is compared for each category, and ORs for RTC responsibility are calculated for drug users. Blood samples should be used for all categories of RTC responsibility and the samples should be taken immediately after the RTC. The second-best alternative is to collect samples of oral fluid. If collecting urine samples, drug intake during the last days or weeks is detected, not only active drug exposure at the time of the RTC. Some responsibility studies are using self-reported use of drugs, which may introduce difficulties due to underreporting of drug intake, incorrect categorization of active drug exposure, or incorrect reporting of RTCs and RTC responsibilities.

As with case-control studies, a large number of psychoactive substances should be included in the analysis of blood samples to eliminate cases with additive effects due to multidrug use or combinations of alcohol or drugs. Ideally, drug concentrations in blood at the time of the RTC should be included in data analysis. However, this is difficult because of few cases within each relevant drug-concentration interval.

The judgment of responsibility, including any police judgments, may easily be biased, for example by suspicion or knowledge about current or previous alcohol or drug use, previous RTC involvement, traffic violations, or criminal records. It is therefore important that this judgment is done in accordance with predefined criteria [28,103,108].

A potential difficulty is that RTC-involved drivers who are judged to have little or no responsibility for the RTC might not represent randomly selected drivers because they fail to avoid an RTC. This may be related to differences in significant confounding factors regarding personality, sleep deprivation, alertness, health, alcohol or drug use, etc., and may introduce an error in risk estimates.

Table 3. Case-control studies using questionnaires or registries (cases were drivers injured or involved in RTCs)

Authors, year Country, ref.	No. of cases crash outcome	Participation rate (%)[a]	No. of controls	Participation rate (%)[a]	Data source[b]	Substances assessed[c]	Covariates[d]
Blows et al., 2005 New Zealand [15]	571 involved in injurious or fatal RTC	92.8	588 random	78.8	Alcohol: B or BR Cannabis: Q	can[e]	age, alc, bel edu, eth, exp pas, sex, spe tim, veh
Chang et al., 2012 Taiwan [24]	5,183 injured	n/a	31,093 matched by age, sex, year	n/a	National health ins. research DB	and[f], anp ben[f], zhy[f]	com, nop psy, urb
Delaney et al. 2005, Canada [27]	5,579 age 67–84 involved in injurious RTC	n/a	12,911 age 67–84 not involved in injurious RTC	n/a	Driver ins. & health ins. DB	war	age, dis, dru rec, sex, urb
Etminan et al. 2004, Canada [36]	5,579 age 67–84 involved in injurious RTC	n/a	13,300 age 67–84 drivers	n/a	Automobile & health ins. DB	lit[f], caa	age, dru, exp geo, rec, sex
Gomes et al., 2013 Canada [50]	5,300 injured	n/a	5,300 matched	n/a	Prescription & health DB	opi[f]	age, dru, pat ppv, sex
Hemmelgarn et al. 2006, Canada [58]	5,579 age 67–84 involved in injurious RTC	n/a	13,300 age 67–84	n/a	Car ins. & health DB	adb[f]	age, geo, ins rec, sex
Johnell et al., 2014 Sweden [63]	30,845 age 50–80 involved in non-alcohol injurious RTC	n/a	123,380 matched by age, sex, geo	n/a	Prescription & RTC DB	ben[f]	alc, age, dru mar, occ, sex
McGwin et al. 2000, US [83]	447 age 65+ involved in RTC	79.8	454 matched by age, sex	74.1	Q	ace[f], adb, anc[f] and, bet, ben nsa[f]	age, eth, exp sex
Ravera et al., 2011 Netherlands [101]	3,963 injured	n/a	18,828 matched	n/a	Prescription & RTC DB	and[f], anp, anx[f] hyp[f], sed	dru

[a] n/a = not applicable or not known.
[b] Abbreviations for data sources: B = blood; BR = breath; DB = database or registry; Q = questionnaire or interview.
[c] Abbreviations for substances: ace = angiotensin converting enzyme inhibitors; adb = antidiabetics; anc = anticoagulants; and = antidepressants; anp = antipsychotics; anx = anxiolytics; ben = benzodiazepines; bet = beta blockers; caa = carbamazepine; can = cannabinoids; hyp = hypnotics; lit = litium; nsa = non-steroidal anti-inflammatory drugs; opi = opioids; sed = sedatives; war = warfarin; zhy = z-hypnotics (zolpidem, zopiclone).
[d] Abbreviations for covariates: age = age of driver; alc = alcohol used; bel = seatbelt use; com = comorbidity score; dis = disease or health status; dru = drug(s) used; edu = education grade; eth = ethnicity; exp = driver experience or milage; geo = geographical area; ins = insulin use; mar = marital status; nop = non-psychiatric outpatient visits; occ = occupational status; pas = passengers in car; pat = previous alcoholism treatment; ppv = previous physician visits; psy = psychiatric outpatient visits; rec = previous driving records; spe = speed; tim = time of day or week; urb: urbanity; veh = vehicle age.
[e] Statistically significant association was reported for some groups of drivers.
[f] Statistically significant association between drug use and RTC was reported.

Another problem is the inclusion of drivers involved in single-vehicle RTCs, who are virtually all responsible for their RTCs. It may not be relevant to compare those drivers with nonresponsible drivers, who are almost exclusively included in multiple-vehicle RTCs.

A review of previous responsibility studies and difficulties and faults has recently been published [108]. Difficulties were often related to selection procedures, the definition of responsibility, the use of undocumented factors when assessing responsibility, lack of blinded exposure assessment, varying or missing data on the proportion of responsible drivers, and lacking discussion of confounding and mitigating factors.

Case-crossover studies are comparing the number of RTCs for each individual during periods of drug use with periods without drug use. Each person in the study is both a case and his own self-matched control. This study design eliminates the need for matching cases and controls regarding a number of confounding factors that may affect the RTC risk. Periods of drug exposure may be based on either self-reported use or data recorded in prescription registries, whereas data on RTCs may be based on self-reports or RTC registries. An important difficulty with this study design is that nontreated illness during periods with no drug use may bias the risk calculations.

A list of responsibility and case-crossover studies published in English after 1998 is presented in **Table 4**.

Table 4. Studies of only RTC-involved drivers

Authors, year country, ref.	Methodology	Drivers	Data source[a]	Substances analyzed[b]	Substances assessed[b]	Covariates[c]
Asbridge et al. 2014 Canada [2]	Case-crossover	860 injured in RTC	B, Q	alc	can[d]	ben, coc
Barbone et al. 1998 UK [6]	Case-crossover	19,386 RTC-involved	Prescription & RTC DB	n/a	and, ben[d]	
Bedard et al. 2007, US [7]	Recorded unsafe driving action[e]	32,543 killed in RTC	B or U FARS DB	alc, amp, ben, can coc, opi, opd	can[f]	age, alc, rec, sex
Corsenac et al. 2012, France [26]	Responsibility	72,685 involved in injurious RTC	Police & health Ins. DB	n/a	bup[d], met[d]	age, alc, dis, dru geo, inj, occ, sex tim, vet
Drummer et al. 2004, Australia [29]	Responsibility	3,398 killed in RTC	B, police crash reports	alc, amp, ben, can coc, ecs, opi	ben, can[d] opi, sti[g]	age, alc, geo, sex sin, yea
Dubois et al. 2008, US [32]	Recorded unsafe driving action[e]	72,026 involved in non-alcohol fatal RTC	B or U FARS DB	alc, amp, ben, can coc, opi, opd	ben[f,h]	age, dru, rec, sex
Dubois et al. 2010, US [31]	Recorded unsafe driving action[e]	72,026 involved in non-alcohol fatal RTC	B or U FARS DB	alc, amp, ben, can coc, opi, opd	opi[f,g]	age, dru, rec, sex
Gadegbeku et al. 2011, France [41]	Responsibility	6,932 involved in fatal RTC	Alcohol: B if BR+ Drugs: B if U+ RTC DB	alc, amp, can, coc opi	amp, can[d] coc, opi	age, sex
Gates et al. 2013, US [42]	Recorded unsafe driving action[e]	8,325 male truck drivers involved in non-alcohol fatal RTC	B or U FARS DB	alc, amp, ben, can coc, opi, opd	can, opi[f] sti[f]	age, dru, rec
Gibson et al. 2009, UK [44]	Case-crossover Case-series	49,821 involved in RTC	Health DB	n/a	and[h,i], anh[i] ben[d], bet, hyp[h,i], opi[d]	
Laumon et al. 2005, France [71]	Responsibility	10,748 killed in RTC	Alcohol: B if BR+ Drugs: B if U+ RTC DB	alc, amp, can coc opi	can[d]	age, alc, tim, vet
Longo et al., 2000 Australia [76]	Responsibility	2,500 injured in RTC	B, police crash reports	alc, ben, can, sti	can, sti	
Longo et al., 2001 Australia [77]	Responsibility	2,500 injured in RTC	B, police crash reports	alc, ben, can, sti	ben[d]	
Lowenstein & Koziol-McLain 2001, US [78]	Responsibility	414 injured in RTC	U RTC DB	alc, amp, bar, ben can, coc, lsd, mep opi, pcp, xyl	can	age, bel sex, tim
Meuleners et al. 2011, Australia [84]	Case-crossover	616 age 60+ injured in RTC	Prescription & hospital DB	n/a	and[d], ben[d] opi[d]	age, dis, eth, geo mar, sex
Orriols et al. 2011, France [94]	Case-crossover Responsibility	72,685 drivers involved in injurious RTC	Health ins. & police DB police reports	n/a	hyp[h]	age, alc, dis, dru geo, occ, sev, sex tim, vet
Orriols et al. 2012, France [95]	Case-crossover Responsibility	72,685 drivers involved in injurious RTC	Health Ins. & police DB police reports	n/a	and[d]	age, alc, dis, dru geo, occ, sev, sex tim, vet
Orriols et al. 2013, France [93]	Case-crossover Responsibility	72,685 drivers involved in injurious RTC	Health ins. & police DB police reports	n/a	ane[d]	age, alc, dis, dru geo, occ, sev, sex tim, vet
Orriols et al. 2013, Canada [96]	Case-crossover	2,919 age 66–84 Antidepressants used at day of RTC	Car ins. & health ins. DB	n/a	and[d]	
Poulsen et al., 2014 New Zealand [98]	Responsibility	1,046 killed in RTC	B, police crash reports	alc, amp, ben, can ecs, opd, opi	can	age, lic, sex, sin urb, vet
Rapoport et al. 2011, Canada [100]	Case time-to-event	159,678 drivers age 65+	Health ins. & RTC DB	n/a	and[g], anf anp[d], ben[d] mul[d], ppi	dru, lic, sex

Table 4. (Continued)

Authors, year country, ref.	Methodology	Drivers	Data source[a]	Substances analyzed[b]	Substances assessed[b]	Covariates[c]
Reguly et al. 2014, US [102]	Recorded unsafe driving action[e]	8,325 male truck drivers killed in non-alcohol RTC	B or U FARS DB	alc, amp, ben, can coc, opd, opi	opi[f]	age, dru, rec sex
Sagberg, 2006 Norway [107]	Responsibility	4,448 RTC-involved	Q	n/a	and[d]	age, dis, exp
Soderstrom et al. 2005, US [111]	Responsibility	2,537 injured in RTC	Alcohol: B Drugs: U Hospital DB RTC DB	Not specified	can, coc[d]	age, sex
van Elslande et al. 2012, France [114]	Recorded unsafe driving action[e]	174 THC-positive & 174 matched killed drivers (no alcohol or drugs detected)	B**,** RTC DB	alc, can, opd	can[f]	age, sex
Yang et al., 2011 Taiwan [122]	Case-crossover	1 million	Health ins. research DB	n/a	ben[d], zhy[d]	

[a] Abbreviations for data sources: B = blood; BR = breath; DB = database or registry; Q = questionnaire or interview; U = urine; FARS = Fatality Analysis Reporting System, an US database operated by the National Highway Traffic Safety Administration.
[b] Abbreviations for substances: alc = alcohol; amp = amphetamines; and = antidepressants; ane = antiepileptics; anf = antifungal drugs; anh = antihistamines; anp = antipsychotics; bar = barbiturates; ben = benzodiazepines; bet = beta blockers; bup = pubrenorphine; can = cannabinoids; coc = cocaine/metabolites; ecs = ecstacy (MDMA); hyp = hypnotics; mep = meprobamate; met = methadone; mul = multiple drug use; opd = other psychoactive drugs; opi = opioids; ppi = proton pump inhibitors; sti = stimulants; xyl = xylene; zhy = z-hypnotics (zolpidem, zopiclone); n/a = not applicable.
[c] Abbreviations for covariates: age = age of driver; alc = alcohol used; bel = seatbelt use; dis = disease; dru = drug(s) used; eth = ethnicity; exp = driver experience or milage; geo = geographical area; inj = previous injuries; lic = driver license status; mar = marital status; occ = occupational status; rec = previous driving records; sev = injury severity; sin = single vehicle crash; tim = time of day or week; urb: urbanity; vet = vehicle type; yea = year of crash.
[d] Statistically significant association between drug use and RTC responsibility.
[e] Proxy measure for RTC responsibility.
[f] Statistically significant association between drug use and unsafe driving action.
[g] Statistically significant association for some groups of drivers.
[h] Statistically significant association for some drugs.
[i] For long-term use.

II. RESULTS

A. Study Quality

Many large studies based on registry data have been performed. The quality of those studies depends primarily on the quality and completeness of the registries, both regarding RTCs and drug use. The individual use of alcohol, illicit drugs, and medicinal drugs obtained on the illicit market is not included in those registries and may cause a study bias.

Many large population surveys have also been performed. It is well known that both the use of drugs and involvement in RTCs is often underreported, particularly the use of illicit drugs [1,37,54,89,113]. In many studies, the participants have not been asked about the use of alcohol or important drug groups, only selected drugs, e.g., only cannabis. Most surveys have not included factors related to alcohol or drug behavior, other behavioral factors, or personality factors, which may be important confounders.

The largest and best-performed case-control studies on drugs and RTC involvement were part of the European Project DRUID (Driving Under the Influence of Drugs, Alcohol and Medicines) [12,56,57] and complied with most of the recommendations published by Walsh et al. [118]. Some small studies were also well performed; however, the statistical power was weaker in those studies due to small numbers of cases and controls.

Three large case-control studies have also been performed in the US [25,74,106]. However, two of them, Li et al. [74] and Romano et al. [106], were not in accordance with the most critical recommendations for research on drugged driving [118]. The cases were selected from the US Fatality Analysis Reporting System (FARS) database, whereas the controls were selected from the 2007 roadside survey [68]. The FARS database has limitations that do not allow calculation of reliable estimates of the risk of RTC involvement resulting from drug use [13,25]. This is due to many factors, including inconsistent drug testing between states, a bias in selecting cases for drug testing

(only about half of fatal-RTC drivers are tested for drugs), failure to record all drug findings in the database, and data on drug findings were based on either blood or urine testing with cutoff concentrations not specified. In addition, the cutoff concentrations in blood from cases and oral fluid from controls were not equivalent; for some drugs the cutoffs for oral fluid testing were therefore too low and for others too high compared to those used for blood. Those issues introduced unpredictable errors in the studies. The calculated ORs would certainly have been different if only blood samples had been collected for cases and controls.

The third large US case-control study was performed in Virginia Beach, VA [25]. This study might have been better designed, but details had not been published by the time this review was prepared.

Some other studies used partly blood and partly urine samples and in one study only sweat samples were collected from some participants; this makes interpretation of data difficult.

Problems mentioned above pertaining to study quality are referred to for some of the studies that are presented below.

We have primarily included peer-reviewed articles. We have only included studies that accurately specified drugs or drug groups; studies on the association between RTCs and the use of "prescribed drugs", "psychoactive drugs", or "CNS drugs" without specifying which groups were excluded. Studies from 1998 discussed in the previous review article by Mørland [90] have not been included in this update.

B. Road Traffic Crash (RTC) Risk Associated with Drug Use

1. Benzodiazepines and z-Hypnotics

Engeland and co-workers [35] performed a population study using Norwegian prescription and RTC databases (*see* Table 1). They found an increased RTC risk during the first seven days after patients started using benzodiazepines (standardized incidence ratio [SIR] of 2.9, 95% CI 2.5–3.5 for tranquillizers and SIR 3.3, 95% CI 2.1–4.7 for hypnotics). A similar increased risk was found by Bramness and co-workers [20] for patients starting to use diazepam (SIR 2.8, 95% CI 2.2–3.6).

Gustavsen et al. [52] used Norwegian databases to study RTCs during the first week after a hypnotic drug was dispensed. The largest risk increase was observed for flunitrazepam (SIR 4.0, 95% CI 2.4–6.4), followed by nitrazepam (SIR 2.7, 95% CI 1.8–3.9), and lowest for z-hypnotics (zopiclone and zolpidem; SIR 2.3, 95% CI 2.0–2.7). Lai and co-workers [69] studied patients using zolpidem in Taiwan and found increased risk for major injury (hazard ratio (HR) 1.67, 95% CI 1.19–2.34); the risk increased with increasing dosage.

Bernhoft et al. [12] and Hels et al. [56,57] (*see* Table 2) found in the two DRUID case-control studies a significant association between the use of benzodiazepines or z-hypnotics and being injured (OR 1.77, 95% CI 1.16–2.69) or killed (OR 4.59, 95% CI 3.28–6.43) [56,57] in RTCs. The Belgian part of the DRUID case-control studies published by Kuypers and co-workers [66] found a significant association between the use of z-hypnotics and being injured (crude OR 6.45, 95% CI 1.63–25.52) but no significant association for benzodiazepines.

Gjerde and coworkers [46] found significant association between the use of only one benzodiazepine drug and being killed in an RTC (OR 8.8, 95% CI 4.7–16.5), and similar results for using only diazepam (OR 6.4, 95% CI 2.5–16.7). No significant association was found for the use of only zopiclone and fatal injury among drivers.

Significant associations between benzodiazepine use and being injured or killed in RTCs were found in case-control studies by Assum et al. [4] (OR 12.6, 95% CI 1.3–122.8), Brault et al. [23] (OR 3.9, 95% CI 2.5–6.1), Hou et al. [59] (OR 3.41, 95% CI 1.76–6.70), Mathijssen and Houwing [82] (OR 2.98, 95% CI 1.31–6.75), Movig et al. [87] (OR 5.05, 95% CI 1.82–14.04) and Mura et al. [88] (OR 1.7, 95% CI 1.2–2.4).

Chang and co-workers [24] found in a population-based case-control study (*see* Table 3) an adjusted OR of 1.64 (95% CI 1.43–1.88) for an RTC after one week's use of benzodiazepines and an OR of 1.37 (95% CI 1.06–1.75) for z-hypnotics. Johnell et al. [63] found in a Swedish study an OR of 1.26 (95% CI 1.17–1.36) for involvement in an injurious RTC after using benzodiazepines and no combination with other drugs.

Ravera et al. [101] performed a case-control study in the Netherlands using prescription data linked with police RTC data and driving license data. A significant association was found between the use of hypnotic benzodiazepines with intermediate half-life and involvement in an RTC (OR 6.44, 95% CI 1.44–28.78), but no significant associations were found for other hypnotics or sedatives.

Gibson et al. [44] (*see* Table 4) performed a case-series study in the UK; an incidence rate ratio (IRR) of 1.94 (99% CI 1.62–2.32) was found for benzodiazepines in the first four weeks of treatment and increased with extended exposure. Short-term use of z-hypnotics was not associated with an increased RTC risk, but longer-term use was associated with a modest increased risk (IRR 1.37, 95% CI 1.05–1.79).

Longo et al. [77] found in a responsibility study that drivers who tested positive for benzodiazepines had a higher culpability rate than drug-free drivers. They also found a significant linear relationship between benzodiazepine concentration and culpability for drivers who tested positive for benzodiazepines alone.

Meuleners and co-workers [84] performed a population-based case-crossover study of older drivers based on data from registries and found that benzodiazepine users had an OR of 5.3 (95% CI 3.6–7.8) for hospitalization due to RTC.

Rapoport et al. [100] found a significant association between benzodiazepine use and RTC involvement among elderly drivers (HR 1.05, 95% CI 1.03–1.07) in a case-only, time-to-event study.

Yang et al. [122] performed a case-crossover study based on data from the Taiwanese health insurance research database and found an OR for RTCs of 1.74 (95% CI 1.25–2.43) after taking one defined daily dose of zolpidem, OR 1.55 (95% CI 0.98–2.45) for zopiclone, OR 1.74 (95% CI 1.26–2.40) for long half-life benzodiazepines, and OR 1.13 (1.04–1.23) for short half-life benzodiazepines.

Dubois et al. [32], using the FARS database, studied unsafe driving actions among drivers killed in RTCs. Compared with drivers not using benzodiazepines, drivers taking intermediate or long-half-life benzodiazepines demonstrated increased odds for an unsafe driving action from ages 25 to 55. Drivers taking short-half-life benzodiazepines did not demonstrate increased odds.

Orriols et al. [94] found in a French registry-based responsibility study that the risk for being responsible for an RTC was higher in users of benzodiazepine hypnotics (OR 1.39, 95% CI 1.08–1.79) and among drivers to whom a dosage of more than one pill of zolpidem a day had been dispensed during the five months before an RTC (OR 2.46, 95% CI 1.70–3.56); no association was found for zopiclone and risk of an RTC.

Compton and Berning [25] found that RTC-involved drivers were significantly more likely to test positive for sedatives in the recent large case-control study in Virginia Beach, VA. However, if adjusting for age, gender, ethnicity, and presence of alcohol, the OR for RTC involvement was not statistically significant. Drummer and co-workers [29] found no significant association between benzodiazepine use and RTC responsibility; however, the number of cases was small, so the study had low statistical power.

Gjerde et al. [48] found, in another small study, no significant associations between a single use of diazepam, any benzodiazepine, or zopiclone, probably because of lower statistical power. However, significant associations were found for any use of those substances (alone or in combination with other drugs or alcohol).

McGwin et al. [83] found, in an American case-control study based on registry data, a weak although not statistically significant association; OR of 5.2 (95% CI 0.9–30.0).

2. Cannabis

Asbridge et al. [3] (Table 1) studied the association between self-reported driving under the influence of cannabis with RTCs among senior students. A statistically significant association was found; the adjusted OR was 2.39 ($p < 0.001$).

Fergusson and Horwood [38] studied the association between cannabis use and RTC involvement in a young birth cohort in New Zealand. They found a statistically significant relationship between reported annual cannabis use and RTC rates ($p < 0.001$). They concluded that the risk appeared to reflect the characteristics of the cannabis users rather than the effect of cannabis use on driver performance. In a second study of the same cohort published seven years later [39], the investigators found a marginally significant association ($p = 0.064$) between driving under the influence of cannabis and RTCs after adjustment for annual distance driven and self-reported risky behaviors.

Gerberich et al. [43] found a significant association between current marijuana use and hospitalization due to RTCs among men (IRR 1.96, 95% CI 1.23–3.14) but no statistically significant association for women (IRR 1.23, 95% CI 0.71–2.05). However, the total number of RTCs was only 188 (100 for men and 88 for women), so the statistical power of this study was not very high.

Mann et al. [79] found a significant association between self-reported cannabis use more than once a week and self-reported RTC involvement (OR 2.76, 95% CI 1.50–5.08) in a Canadian population survey. They also found a significant association between self-reported driving within an hour after cannabis use and RTC (OR 2.61, 95% CI 1.45–4.68). They found similar results in a study performed three years later using a larger dataset [80]; the OR for self-reported collision after cannabis use was 1.84 (95% CI 1.23–2.76).

In a Spanish national survey, Pulido et al. [99] found a significant association between self-reported cannabis use more than four days per week and self-reported RTC injury (OR 1.6, 95% CI 1.0–2.6) but no significant association for less frequent use.

In a study in Wales using postal questionnaires, Wadsworth and co-workers [117] found that cannabis use during the previous year was associated with involvement in RTCs (OR 1.92, 95% CI 1.04–3.54).

The DRUID case-control studies published by Bernhoft et al. [12] and Hels et al. [56,57] (Table 2) found a significant association between THC and RTC injury (OR

1.91, 95% CI 1.15–3.17), but no statistically significant association with fatal RTCs (OR 1.25, 95% CI 0.45–3.51) [12,56]. For the Belgian part of the DRUID study using blood samples from cases and controls [66], a very high OR of 13.40 (95% CI 3.95–45.42) for involvement in injurious RTCs was calculated.

In American case-control studies, Li et al. [74] and Romano et al. [106] found significant crude ORs of 1.83 (95% CI 1.39–2.39) and 1.55 (95% CI 1.42–1.94), respectively. Compton and Berning [25] found that THC was associated with a significantly elevated risk of RTCs, with a crude OR of 1.25. However, when adjusting for age, gender, ethnicity, and presence of alcohol, the OR was not statistically significant.

Beirness et al. [9] found in a case-control study using data from British Columbia, Canada, an OR of 4.95 (95% CI 3.70–6.62). The study is not very well described and the cutoff concentrations in oral fluid for controls and blood for cases were most likely not equivalent.

Brault et al. [23] found in a Canadian case-control study using urine samples an OR for fatal RTCs associated with cannabis alone of 1.6 (96% CI 1.1–2.4); for all cannabis cases (with or without other substances) the OR was 4.5 (95% CI 3.3–6.0).

Mura et al. [88] found in a French case-control study a significant association between cannabis and RTC injury for THC (OR 2.5, 95% CI 1.5–4.2) when analyzing blood, urine, or sweat samples.

Marquet et al. [81] found significant difference in cannabis findings in urine samples from female drivers involved in RTCs in France compared to non-trauma patients ($p = 0.02$) but not for male drivers; however, the number of cases ($n = 296$) and controls ($n = 278$) were low, giving low statistical power, and the study was flawed as alcohol and sedative therapeutic drugs were not analyzed.

Blows and coworkers [15] (Table 3) found in a population-based case-control study in New Zealand based on self-reported data that there was no significant association between acute marijuana intake and RTC injury (OR 0.8, 95% CI 0.2–3.3), whereas there was a strong association between habitual use and RTC injury (OR 9.5, 95% CI 2.8–32.3). The authors concluded that the nature of this relationship was unclear.

Asbridge et al. [2] (Table 4) found in a Canadian case-crossover study using blood sample analysis and self-reported data that cannabis used was associated with a fourfold increased odds of an RTC (OR 4.11, 95% CI 1.98–8.52), whereas a regression relying on self-reports measures found no significant association.

Bedard and coworkers [7] found in a study of drivers killed in RTCs using data from the American FARS database that the presence of cannabis in biological samples was associated with significantly increased odds for potentially unsafe driving action (OR 1.29, 95% CI 1.11–1.50).

Drummer and coworkers [29] found in an Australian responsibility study that drivers with THC in their blood had a significantly higher likelihood of being culpable for an RTC than drug-free drivers (OR 2.7, 95% CI 1.02–7.0); for drivers with THC concentrations of 5 ng/mL or higher the OR was 6.6 (95% CI 1.5–28.0). Gadegbeku et al. [41] found an OR of 1.89 (95% CI 1.43–2.51) and Laumon et al. [71] found an OR of 3.32 (95% CI 2.63–4.18) for cannabis in similar responsibility studies in France; ORs in relation to THC concentration intervals were presented in both studies.

Van Elslande et al. [114] found that drivers who were killed in RTCs with THC in blood (and no detection of other drugs or alcohol) had significantly higher rates of driving failures than matched controls, i.e., fatally injured drivers without any alcohol or drugs detected in their blood test. The THC-positive drivers had significantly lower levels of attention ($p < 0.01$) and significantly higher level of risky driving ($p < 0.01$) as well as significantly higher frequencies of other failures.

Assum et al. [4] found no significant association between cannabis use and RTC involvement in their case-control study. However, the number of cases ($n = 87$) and controls ($n = 410$) were far too low to give sufficient statistical power; in addition, the cutoff concentrations in oral fluid and blood were not equivalent.

Gjerde et al. [46,48] found no significant associations between THC and fatal RTCs after using only cannabis in two Norwegian studies (OR 0.9, 95% CI 0.1–7.3; and OR 1.9, 95% CI 0.8–4.6), probably due to low statistical power, but significant associations if also including cases and controls with THC in combination with other drugs (OR 8.6, 95% CI 3.9–19.3; and OR 8.9, 95% CI 5.2–15.4).

Gates and co-workers [42] found in a study of data on truck drivers involved in fatal RTCs based on the American FARS database an OR of 1.14 (95% CI 0.84–1.53) for performing an unsafe driving action associated with cannabinoids, which was detected by either blood or urine testing.

Mathijssen and Houwing [82] found, in a Dutch study using blood samples from cases and urine or blood samples from controls, no statistically significant association with RTCs. Urine samples may be positive for cannabinoids for weeks after use. Thus, urine samples are particularly unsuitable for case-control studies on the association between cannabis use and RTCs, except if only urine samples are collected from both cases and controls. Therefore, this study design gives incorrect risk estimates. The number of included cases was low ($n = 184$).

Movig et al. [87] found no significant association between cannabis use and RTC involvement in their case-control study. They collected either blood or urine from cases and controls. The fraction giving urine samples was significantly higher among controls (85%) than cases (39%), thereby underestimating the calculated ORs because urine samples are positive for drugs for a significantly longer time period than blood samples after drug use. In addition, the number of cases was low (n = 110), giving poor statistical power.

Woratanarat et al. [121] collected urine from both cases and controls. Very few samples from cases and controls were positive for cannabis, and no significant association between cannabis use and RTCs was found. As only urine samples were used, the study did not determine cannabis use immediately prior to the RTC but rather cannabis use during the last week(s).

Longo et al. [76] found no significant association between THC and responsibility for an RTC in an Australian study. In the US, Lowenstein and coworkers [78] found no significant association between cannabis in urine and RTC responsibility.

Poulsen and coworkers [98] found only a weak association, although not statistically significant, between THC alone in blood and culpability for fatal RTCs in New Zealand (OR 1.3, 95% CI 0.8–2.3) when studying 1,046 fatally injured drivers.

Soderstrom and coworkers [111] found neither a significant association between cannabis in urine and culpability for an RTC in a study of more than 2,500 drivers in Maryland.

3. Opioids

A Norwegian population study published by Engeland et al. [35] (Table 1) linking data from prescription registries with RTC databases found increased risk for involvement in RTCs among patients using natural opium alkaloids (SIR 2.0, 95% CI 1.7–2.4). Another Norwegian study by Bachs et al. [5] found significant increased RTC risk among patients using codeine (SIR 1.9, 95% CI 1.6–2.2) but no significant accident risk associated with the use of tramadol (SIR 1.5, 95% CI 0.9–2.3). Bramness et al. [19] found that male opioid maintenance treatment patients using methadone had increased RTC risk (SIR 2.4, 95% CI 1.5–3.6) but no significantly increased risk was observed for female patients.

Bernhoft, Hels, and coworkers (Table 2) [12,56,57] found in the European DRUID case-control studies an OR for being injured after using medicinal opioids of 7.37 (95% CI 4.99–10.88) and for being killed an OR of 4.07 (95% CI 2.14–7.72) [12, 56]. For illicit opiates, the OR was not statistically significant for injured drivers, whereas for killed drivers, the OR was 10.04 (95% CI 2.04–19.32).

Significantly increased risks for RTCs were also found in case-control studies by Brault et al. [23] for all opiate cases (OR 3.1, 95% CI 1.5–6.5), Mura et al. [88] for morphine (OR 8.2, 95% CI 2.5–27.3), Woratanarat et al. [121] for morphine (OR 27.97, 95% CI 9.77–80.08), Mathijssen and Houwing [82] for morphine/heroin (OR 32.4, 95% CI 1.78–592) and Li et al. [74] for narcotic analgesics (crude OR 3.03, 95% CI 2.00–4.48).

Gomes et al. [50] (Table 3) found in a Canadian population-based nested case-control study a statistically significant association between opioid dose and risk for RTC trauma among drivers; the OR was 1.29 (95% CI 1.06–1.57) for moderate doses and 1.42 (95% CI 1.15–1.76) for high doses.

Meuleners and co-workers [84] (Table 4) found in an Australian case-crossover study based on prescription and hospital databases a significant risk for injurious RTCs among older patients using opioid analgesics (OR 1.5, 95% CI 1.0–2.3). Reguly and coworkers [102] found in a study using data from the American FARS database that male truck drivers using opioid analgesics involved in fatal RTCs had greater odds of committing unsafe driver actions (OR 2.80, 95% CI 1.64–4.81).

Corsenac et al. [26] (Table 4) used data from three French national databases and performed responsibility and case-crossover analyses. Drivers who had been exposed to methadone and/or buprenorphine on the same day as an RTC had significantly higher odds for being responsible for the crash (OR 2.02, 95% CI 1.40–2.91).

Dubois and coworkers [31] found, in a study based on data from the American FARS database, that female drivers who tested positive for opioid analgesics demonstrated increased odds for performing an unsafe driving action from age groups 25–34 years (OR 1.35, 95% CI 1.05–1.74) to 55–64 years (OR 1.30, 95% CI 1.07–1.58); for male drivers this was true from age groups 25–34 years (OR 1.66, 95% CI 1.32–2.09) to 65–74 years (OR 1.39, 95% CI 1.17–1.67).

Gibson and coworkers [44] found, in a case-series study using a British health database, that initiation of opioid treatment was associated with an increased risk of RTCs (IRR 1.70; 99% CI 1.39–2.08).

Gates et al. [42] found in their study of truck drivers involved in fatal RTCs that those who were positive for opioid analgesics had higher odds for committing an unsafe driving action (OR 1.63, 95% CI 1.12–2.35).

Assum et al. [4] found no statistically significant association between opiate use and RTC involvement in a small Norwegian study. Compton and Berning [25] reported no significant association between the use of

narcotic analgesics and RTC involvement. Romano et al. [106] found no significant association between the use of narcotic analgesics and fatal crash (crude OR 1.14, 95% CI 0.92–1.61). Marquet and coworkers [81] found no significant association, but the study was flawed because analysis of alcohol and sedative therapeutic drugs was not performed.

Kuypers and coworkers [66] found an OR for being injured of 3.91 (95% CI 0.97–8.68) after analyzing blood samples from cases and controls.

Movig et al. [87] found a positive association between opioids and RTCs, although not statistically significant (OR 2.35, 95% CI 0.87–6.34).

In responsibility studies, Drummer et al. [29] and Gadegbeku et al. [41] did not find any significant association between opiates and culpability; however, the statistical power in those studies was low.

4. Stimulants

a. Amphetamines

Bernhoft, Hels, and coworkers (Table 2) found in the European DRUID case-control studies that the use of amphetamines alone was associated with adjusted ORs of 14.15 (95% CI 5.82–34.42) [12,56,57] for being injured and 34.34 (95% CI 13.18–89.49) [12,56] for being killed. Blood samples were collected and analyzed from cases and oral fluid or blood samples from controls using equivalent cutoff concentrations for blood and oral fluid. Gjerde et al. found in two similar studies in Norway adjusted ORs of 20.9 (95% CI 7.3–60.0) [48] and 41.6 (95% CI 12.6–137.1) [46] after using only amphetamine or methamphetamine, while the ORs were 57.1 (95% CI 27.3–119.5) and 76.9 (95% CI 38.7–152.9) for use of amphetamines in total, i.e., with or without other substances. Blood and oral fluid were analyzed with equivalent cutoff concentrations. The latest study included practically the same control material as used in the Norwegian contribution to the DRUID Project and samples from killed drivers for several more years.

Kuypers et al. [66] published results from the Belgian part of the DRUID case-control studies using blood samples from cases and controls. For amphetamines (single use) the crude OR for being injured in an RTC was 54.82 (95% CI 6.09–493.12); an adjusted OR was not calculated.

Brault et al. [23] found in a Canadian case-control study an OR for being killed in an RTC after use of amphetamines of 11.0 (95% CI 2.9–41.3) using urine samples; this included also amphetamines in combination with other substances. Woratanarat et al. [121] found OR of 8.88 (95% CI 4.54–17.39), also based on urine samples from both cases and controls in Thailand.

Assum and coworkers [4] found amphetamines in blood samples from eight cases and none of the controls in a small Norwegian study. In order to calculate the OR, 0.5 unit was added to negatives and positives among cases and controls and 37 negative cases were added to correct for sampling bias. The calculated OR for RTC involvement was then 29.5 (95% CI 1.5–575.6). The statistical power of this study was poor.

Neither Gadegbeku et al. [41] nor Movig et al. [87] found any significant association in a French responsibility study and a Dutch case-control study. Gadegbeku and coworkers found only 54 drivers positive for amphetamines in blood samples in a responsibility study (OR 1.54, 95% CI 0.66–3.56), which gave a fairly low statistical power. Movig and coworkers collected either blood or urine from cases and controls; the fraction giving urine samples was significantly higher among controls (85%) than cases (39%), thereby underestimating the calculated ORs because urine samples are positive for drugs for a significantly longer time period than blood samples after drug use. Another difficulty was that only 7 out of 110 cases were positive for amphetamines and 13 out of 816 controls, giving low statistical power and a wide confidence interval (OR 2.10, 95% CI 0.66–6.73).

b. Cocaine

In a Spanish population study using questionnaires, Pulido et al. [99] (Table 1) found a significant association between weekly cocaine use and involvement in nonfatal RTC injury (OR 2.8, 95% CI 1.1–7.1) but not for less frequent use. Stoduto et al. [112] found in a similar Canadian study a significant association between self-reported cocaine use last year and involvement in an RTC (OR 2.11, 95% CI 1.06–4.18).

The DRUID case-control studies (Table 2) found no significant association between the use of cocaine and injuries; the adjusted OR was 1.65 (95% CI 0.66–4.16) [12,56,57]. For fatal RTCs the adjusted OR could not be calculated; the crude OR was 22.34 (95% CI 3.66–36.53) [12,56]. Brault et al. [23] found OR of 4.5 (95% CI 1.2–16.3) for the association with fatal RTCs for cocaine alone and 17.2 (95% CI 10.8–27.2) for all cocaine cases altogether based on urine testing.

Soderstrom et al. [111] (Table 4) found in an American responsibility study significant associations between cocaine and RTC injury for male drivers (OR 2.17, 95% CI 1.14–4.13); for female drivers a positive association was also found, although not statistically significant (OR 2.34, 95% CI 0.86–6.35).

Gadegbeku et al. [41] found no significant association based on the calculations of only 34 cocaine-positive cases

in France (OR 1.17, 95% CI 0.45–3.02). Kuypers et al. [66] found only one case and two controls that were positive for cocaine and therefore no significant association. Movig et al. [87] found 10 cases and 16 controls that were positive for cocaine (OR 2.04, 95% CI 0.69–6.09) and thus no significant association based on those low numbers when using a combination of urine and blood samples.

c. Stimulants in Total Rather Than Specified Substances

Li et al. [74] and Romano et al. [106] (Table 2) studied data recorded in the FARS database and data from the American roadside survey of drugs and driving [68]. The two studies reported crude OR for stimulants of 3.57 (95% CI 2.63–4.76) and 1.87 (95% CI 1.45–2.43), respectively, for association with fatal RTCs based on case-control calculations without specifying the cutoff concentrations used. Analytical findings in urine or blood samples from cases and samples of oral fluid from controls were used to calculate the risk. Compton and Berning [25] reported no significant association between the use of stimulants and RTC involvement in a large study in the US.

Gates and coworkers [42] (Table 4) used the FARS database to study the responsibility in fatal RTCs, and found an OR for unsafe driving action of 1.78 (95% CI 1.41–2.26) among stimulant-positive truck drivers compared to stimulant-negative drivers.

In Australian responsibility studies, Longo et al. [76] found that a higher proportion of drivers who tested positive for stimulants in blood were culpable compared to those who were drug-free although not statistically significant, whereas Drummer et al. [29] found an OR of 2.27 (95% CI 0.9–5.6) between stimulant findings and culpability; for truck drivers the calculated OR was 8.83 (95% CI 1.00–78).

5. Antidepressants

Bramness and coworkers [22] (Table 1) found a minor risk increase for antidepressants (SIR 1.4, 95% CI 1.2–1.6 for sedating antidepressants and SIR 1.6, 95% CI 1.5–1.7 for nonsedating antidepressants) in a population study using data from prescription and RTC registries.

Chang and coworkers [24] (Table 3) found an increased risk for RTC after one week's use of antidepressants in a Taiwanese registry-based case-control study (OR 1.71, 95% CI 1.29–2.26). Ravera et al. [101] found significant association between the use of SSRIs (OR 2.03, 95% CI 1.31–3.14) and involvement in RTCs in a similar study.

Meuleners et al. [84] (Table 4) found in a population-based case-crossover study greater risk for RTC involvement among drivers aged 60 or older (OR 1.8, 95% CI 1.0–3.3), highest among patients with a chronic condition (OR 3.4, 95% CI 1.3–8.5).

Orriols et al. [95] used data from the French national healthcare insurance database, the national police database, and police reports to perform responsibility and case-crossover studies. They found a significant association between the risk of being responsible for an RTC and prescription of antidepressants (OR 1.34, 95% CI 1.22–1.47); the case-crossover analysis showed no association with treatment prescription, but the risk of RTCs increased after an initiation of antidepressant treatment (OR 1.49, 95% CI 1.24–1.79) and after a change in antidepressant treatment (OR 1.32, 95% CI 1.09–1.60); the exposure was considered to start on the day following dispensing.

In a case-crossover study of elderly drivers, Orriols et al. [96] found an increased risk of RTCs in drivers with a prescription of antidepressants before their RTC when compared with a prescription of antidepressants four to eight months before the RTC; OR of 1.19 (95% CI 1.08–1.30) to OR of 1.42 (95% CI 1.30–1.55).

Rapoport et al. [100] found a significant association between antidepressant use and RTCs among elderly drivers (HR 1.07, 95% CI 1.05–1.10). A prescription of a benzodiazepine along with the antidepressant was associated with a higher risk (HR 1.23, 95% CI 1.17–1.28), whereas the lack of concomitant benzodiazepine yielded no increase in RTC risk associated with antidepressant use. Similarly, concomitant use of some anticholinergic drugs was associated with significantly higher risk.

Sagberg [107] found a significant risk associated with the use of antidepressants in a Norwegian responsibility study using questionnaires (OR 1.70, $p < 0.04$).

Gibson et al. [44] did not find any elevated risk for RTC involvement when using tricyclic antidepressants in a case-series study; however, extended use of SSRIs was associated with a small increased risk (IRR 1.16, 99% CI 1.06–1.28).

Hou et al. [59] found no significant association in a case-control study in Taiwan. Compton and Berning [25] reported no significant association in a large case-control study in the US. Woratanarat et al. [121] found no significant association in a Thai case-control study based on urine samples. McGwin et al. [83] found no association between antidepressant use and RTC involvement in a study based on interviews and RTC registry.

6. Other drugs

Bramness and coworkers [20] (Table 1) found increased RTC risk during the first week after patients started using carisoprodol (SIR 3.7, 95% CI 2.9–4.8) when linking the Norwegian prescription registry with the RTC registry, and no risk increase for salbutamol. In a similar study [21], no significant risk increase was observed for lithium or valproate, except for young female drivers on

lithium (OR 3.2, 95% CI 1.3–6.6). Etminan et al. [36] also found an increased risk for RTCs among elderly drivers in Canada using lithium (OR 1.80, 95% CI 1.00–3.24).

In a Canadian case-control study based on analysis of biological samples, Brault et al. [23] (Table 2) found significant association between any use of PCP (alone or in combination) and being killed in an RTC (OR 31.4, 95% CI 9.2–107.4).

Engeland et al. [35] (Table 1) found significant association between NSAIDs and RTC involvement (for men: OR 1.6, 95% CI 1.2–2.1; for women: OR 1.5 (95% CI 1.0–2.0). A significant association was also found for penicillins for men: OR 1.4 (95% CI 1.0–2.0); no significant association was found for women. No significant associations were found for the use of beta-blockers and calcium receptor antagonists.

Hemmelgarn et al. [58] (Table 3) found in a Canadian case-control study on antidiabetic drugs based on registry data elevated risk for injurious RTC involvement among elderly patients using insulin (relative risk (RR) 1.4, 95% CI 1.0–2.0) and combined use of sulfonylurea and metformin (RR 1.3, 95% 1.0–1.7).

Rapoport et al. [100] found a significant association between the use of antipsychotic drugs and RTC involvement among elderly drivers (HR 1.17, 95% CI 1.07–1.27). The use of proton pump inhibitors or antifungal drugs was not associated with RTCs.

Skurtveit et al. [110] (Table 1) found in a Norwegian registry study a significant association between RTCs and the use of insulin (SIR 1.4, 95% CI 1.2–1.6); however, the association was not statistically significant for drivers above 35 years of age.

A case-control study based on questionnaires published by McGwin et al. [83] (Table 3) in the US found significant associations between the use of NSAIDs (OR 1.7, 95% CI 1.0–2.6), angiotensin-converting enzyme inhibitors (OR 1.6, 95% CI 1.0–2.7), or anticoagulants (OR 2.6, 95% CI 1.0–73) and RTCs among the elderly. The reasons for these associations are unclear and might be related to the diseases rather than the medication. No significant association was found for other hypertension or heart medication or for the use of insulin, oral hypoglycemics, diuretics, hormones, or arthritis glaucoma medication.

Oriolls et al. [93] (Table 4) found that drivers exposed to prescribed antiepileptic medicines had increased risk of being responsible for an RTC (OR 1.74, 95% CI 1.29–2.34); the association was also significant for the most severe epileptic patients (OR 2.20, 95% CI 1.31–3.69). However, case-crossover analysis found no association between RTC risk and treatment prescription, suggesting that the RTC risk was more likely to be related to the disease with seizures than to the effect of antiepileptic medicines.

Gibson et al. [44] found no effect of receiving a prescription for antihistamines on short-term risk for RTCs, but extended use was associated with increased risk (IRR 1.21; 99% CI 1.04–1.41). They found no significant association for the use of beta-blockers.

Other studies found no significantly increased RTC involvement for barbiturates [23,59] and antihistamines [97,121] and for elderly patients using warfarin [27], carbamazepine [36], or antipsychotics [24].

7. Multiple Drug Use

The DRUID case-control studies [12,56,57] (Table 2) found that the OR associated with multiple drug use was larger than for single drug use except for amphetamines. Kuypers et al. [66] found an OR of 210.97 (95% CI 4.90–9088.71) for combination of stimulants and sedatives and an OR of 13.70 (95% CI 2.95–63.66) for multiple sedatives.

Assum et al. [4] found an OR for RTC involvement of 63.2 (95% CI 3.6–1115.3) after using two drugs and 29.5 (95% CI 1.5–575.6) when using three drugs.

Bogstrand et al. [17] found that the OR for being injured in an RTC after using two drugs was 13.3 (95% CI 4.2–41.3) and after using three or more drugs 38.9 (95% CI 8.2–185.0).

Bogstrand and Gjerde [16] found in a study of drivers arrested for drugged driving (both those arrested after involvement in an RTC and those arrested for other reasons) that multiple drug use was associated with very high risk for arrest, particularly the combination of amphetamines and benzodiazepines. Arrests for drugged driving based on dangerous driving behavior was in this study regarded as a proxy for RTC responsibility.

Gjerde and coworkers found significantly higher OR after using two or more drugs than after using only one drug in case-control studies; after using two or more medicinal drugs the calculated OR was 17.1 (95% CI 5.7–51.9) [48] and OR 28.8 (95% CI 7.3–113.6) [46]; for two or more illegal drugs the OR was 49.7 (95% CI 4.4–561.6) [48]. Highest ORs were found for the combination of amphetamines and benzodiazepines: 98.2 (95% CI 24.9–386.9) [46].

Mathijssen and Houwing [82] found an OR of 24.0 (95% CI 11.5–49.7) for being injured in an RTC after using combinations of drugs, whereas Movig et al. [87] found an OR of 6.05 (95% CI 2.60–14.10) for becoming injured. Li et al. found an OR of 3.41 (95% CI 2.43–4.73) [74].

However, Woratanarat et al. [121] did not find significantly different ORs for multiple and single drug use.

III. DISCUSSION

This article is an update of a review by Mørland published in 2000 [90]. The present review includes only studies published in the English language, primarily in peer-reviewed journals, from January 1998 to February 2015. The results of a large number of investigations have been published during this period, and in general the findings confirm the conclusions made in the previous review.

The European DRUID Project has so far been the most comprehensive study of alcohol, drugs, and RTC risk. The project included large case-control studies [12,56,57,66,101], a responsibility study [41], and other epidemiological and experimental studies that are not reviewed in this article (for an overview, see project deliverables at *http://www.druid-project.eu*).

The DRUID Project and other investigations documented that alcohol constitutes larger RTC risk than the use of any single drug when disregarding the concentrations in blood samples of the substances used. However, the largest increase in RTC risk has been observed for combined use of alcohol and drugs, a combination that has not been discussed in this article.

As mentioned above, a large case-control study was performed recently in Virginia Beach, VA [25]. The prevalence of drugs was found to be 16.0% among RTC-involved drivers and 14.4% among matched drivers in normal traffic. The calculated risks for RTC involvement in that study was significantly lower for both alcohol and drugs than the risks reported in the DRUID Project and many other studies. The reasons for this difference may be discussed when more study details have been published. However, RTC-involved drivers who were too impaired to give informed consent were excluded, as well as RTC-involved drivers below 18 years of age; those two groups were regarded as ineligible. Among the eligible drivers, 5.3% refused to participate. Those three facts might have biased the study significantly, producing incorrectly low drug prevalence among RTC-involved drivers and thus also too low ORs.

The prevalence of drugs in fatally injured drivers in the US (28.3% in 2010) [18] was significantly higher than that reported in the Virginia Beach study (16.0%). This could be related to the inclusion of all types of RTCs, even quite trivial ones, in the study [25], in addition to the factors mentioned above.

A. Benzodiazepines and z-Hypnotics

A total of 28 different analytical epidemiological studies dealt with effects of benzodiazepines and/or z-hypnotics or sedatives in general. In 25 of these studies there was a statistically significant association between benzodiazepines/z-hypnotics (or use of unspecified sedatives) and RTCs. Three studies did not report a significant association, but two of these had low statistical power and one found a weak but not statistically significant association. Thus in sum, analytical epidemiological studies published since 1998 in general found a clear association between use of benzodiazepines and/or z-hypnotics and increased RTC risk.

B. Cannabis

A total of 36 different analytical epidemiological studies have presented data for the effects of cannabis, and 23 found a statistically significant association between cannabis use and RTCs and injuries. The calculated OR was typically in the range 1–4, and was thus similar to the risk observed after starting therapeutic use of a benzodiazepine. Thirteen studies did not report significant associations, but seven of these had either low statistical power or questionable study design. Significant associations as well as lack of significant associations were reported in all three types of study design, i.e., in cohort, case-control, and responsibility/case-crossover.

C. Opioids

A total of 25 different analytical epidemiological studies dealing with the effects of opioids were identified. In 17 of these studies a statistically significant association between opioid use and RTCs was found; in eight studies the association was not statistically significant. However, seven of those studies had either low statistical power and/or questionable design. Significant as well as nonsignificant associations were found in case-control and responsibility/case-crossover studies. The three cohort studies performed found significant associations between prescribed opioids (with the exception of tramadol) and RTC risk. Thus in sum, analytical epidemiological studies performed after 1998 found in most cases an association between opioid use and RTCs.

D. Stimulants

1. Amphetamines

Ten different analytical epidemiological studies have included amphetamines: seven case-control studies and three responsibility studies. Eight of these found statistically significant associations between amphetamine use and RTC risk. The two studies that reported no significant associations still reported a trend. One of these studies most probably underestimated the calculated risk

due to different distribution of blood and urine samples among control and cases. The median OR for RTC involvement in the 10 studies was 18. Thus in sum, the epidemiological studies performed since 1998 report a clear association between amphetamine use and increased RTC risk. Several of these studies found that amphetamine and methamphetamine were associated with higher RTC risk than any other drug, also when not combined with other psychoactive substances.

High concentrations of amphetamines may have harmful effects on self-perception, critical judgment, and risk taking, whereas when the stimulating effects are disappearing, a period associated with fatigue, anxiety, and irritability may occur even if the drug is still present in the body. The risk for involvement in RTCs might be increased both during the stimulated and fatigue periods when taking high doses [75]. It is likely that problematic amphetamine users and addicts constitute a larger traffic safety problem than drivers that occasionally are taking small doses of amphetamines to stay awake and alert during long journeys with little time for resting.

2. Cocaine

Nine different analytical epidemiological investigations studied the effect of cocaine. Five found an association between cocaine use and crashes, whereas 4 studies did not conclude with a significant association. Three of the latter had, however, low statistical power. The ORs reported in all studies were in general lower than those reported for amphetamines. Six of the studies included both amphetamines and cocaine. In all of these, regardless of whether an association between stimulant use and accidents was found or not, the OR-values were always higher for amphetamines. Thus in sum analytical epidemiological studies performed since 1998 found in most cases an association between cocaine use and crash risk. This association appeared, however, to be somewhat weaker than for amphetamines.

E. Antidepressants

Thirteen different analytical epidemiological studies dealing with the effects of antidepressants were identified. In eight of these there was a statistical significant association between use of antidepressants and RTCs; one additional study reported a small risk increase for SSRIs, but not for tricyclic antidepressants. No significant association was observed in four studies. Significant as well as nonsignificant associations were found in case-control and responsibility/case-crossover studies. The only cohort study performed found a statistically significant association. One crossover study indicated that the condition itself (depression) was associated with increased risk, but also that the initial period after start of drug treatment represented a similar association. In sum, the analytical epidemiological studies published since 1998 indicate that there is some association between the use of antidepressants, both tricyclic and SSRIs, and increased RTC risk. The calculated statistically significant ORs were, however, around two or lower.

F. Other Drugs

In general there were few studies on the associations between other drugs and RTCs. Antihistamines were studied in three reports; two of them did not find an association with RTCs, while the third one found a modest increased risk. The most marked risk increase (OR 31.4) was found for the association between RTCs and any use of PCP, and the risk increase after using carisoprodol (SIR 3.8) was higher than for many benzodiazepines.

G. Multiple Drug Use

Twelve different analytical epidemiological studies published since 1998 all found that drug combinations increased the ORs for the association with RTCs compared to single drug use. In some studies the calculated increases in OR were very marked.

CONCLUSIONS

Approximately 15 analytical epidemiological studies published as of 1998 were included in the review published in 2000. In the present paper we have identified 72 analytical epidemiological studies published after those included in the former review. The scientific basis has thus increased substantially within this field of research, and thus constitutes a broader background for the following conclusions.

Epidemiological studies have found that after alcohol, amphetamines are the single substances with highest risk for RTC involvement. Increased RTC risk has also been well documented for cocaine, cannabis, benzodiazepines, z-hypnotics, opioids, and for some antidepressants. Increased RTC risk has also been found for carisoprodol and PCP, although few epidemiological studies have been performed on those substances. Associations with RTCs have been found for some other drugs as well, but it is unclear whether this association was more dependent on the underlying disease than the drug use per se.

The combination of two or more psychoactive drugs has been found to be more risky than single use. However, the combination of psychoactive drugs with alcohol is associated with the highest RTC risk.

The calculated risks for involvement in RTCs associated with the use of different drugs, particularly nontherapeutic use, are closely related to behavioral factors such as risk-taking behavior and impulsivity. The attitudes toward driving after drug use may also vary between countries and between groups within countries. Therefore, the calculated risks associated with drug use may vary between different studies. In addition, abuse of drugs for longer periods can cause somatic and mental changes that may increase the RTC risk as well. Therapeutic drug use may also constitute a lower risk for RTC involvement than nontreated illness. For those reasons it is difficult to determine quantitatively the risk posed by the use of a single drug dose per se in epidemiological studies. The risk depends on who is taking the drug, why, when, how much, how often, and under which circumstances.

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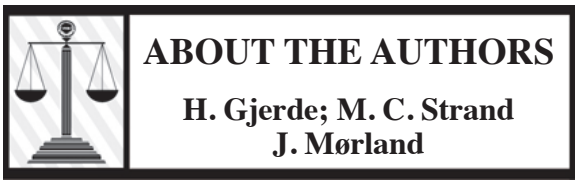

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