Methodologies for establishing the relationship between alcohol/drug use and driving impairment – Differences between epidemiological, experimental, and real-case studies

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ABSTRACT: Experimental, epidemiological and real-case studies have different advantages and limitations when used to study the effect of substance use on the risk for involvement in a road traffic crash. It is easier to perform well-controlled experimental studies than well-controlled epidemiological studies due to difficulties related to selection bias, information bias and confounding. On the other hand, it is difficult or impossible to perform experimental studies using single and repeated substance doses similar to those used by drivers and problematic drugs users. Real-case studies indicate which substances may cause observed impairment and involvement in road traffic crashes and at which concentrations; however, those studies cannot be used to quantify crash risks or determine causality. All three types of studies are needed to obtain a broad and complete picture as they may complement each other when assessing the effects of substance use on road traffic safety.

KEYWORDS: Alcohol, drugs, impairment, research methods, road traffic crash, substance use, traffic safety.

INTRODUCTION

A large proportion of road traffic crashes are caused by driver impairment after using alcohol or other psychoactive substances [167]. Analysis of blood samples from those arrested for driving under the influence (DUI) of alcohol or drugs, or from crash-involved drivers, show variations in detected substances across countries related to regional differences in the use of alcohol, recreational drugs and psychoactive medicines, including problematic use and addiction, as well as differences in attitudes towards driving after using alcohol or drugs [21, 47, 94, 95]. Such differences make comparisons between studies difficult. In general, alcohol is the most commonly used psychoactive substance among drivers, followed by cannabis, central nervous stimulants, such as amphetamines and cocaine, and central nervous depressants, such as sedatives, hypnotics and narcotic analgesics. Multi-substance use is also common among arrested DUI offenders [66, 84, 154].

Most countries have implemented statutory alcohol concentration limits in blood or breath for DUI of alcohol. Many countries have also laws on driving under the influence of drugs other than alcohol, which may either be based on documented impairment, zero tolerance for psychoactive drugs, or concentration *per se* limits in blood [21, 162]. Zero tolerance laws make it a criminal offense to have a drug or metabolite in the body while operating a motor vehicle, and is sometimes regarded as a type of *per se* legislation. This legal framework was constructed, at least in part, to simplify the evidence necessary for a successful prosecution [74].

Standardized research methods are needed in order to generate accurate and reproducible data when studying the effects of alcohol and drugs on the ability to drive safely. The first recommendations and guidelines were published in the 1980-90s [29, 69, 70, 82]. In 2007, an expert meeting was held in Talloires (France) where guidelines on both experimental and epidemiological research were discussed [163]. As an outcome of that meeting, more detailed guidelines and recommendations were developed and published in 2008 [164]. The US National Highway Traffic Safety Administration published a consensus protocol for assessing the potential of drugs to impair driving in 2011, although with less details [85], and a white paper on drugged driving research was published by the Drugged Driving Committee of the Institute for Behavior and Health in the USA, also in 2011 [33]. Finally, the Food and Drug Administration published Guidance for Industry on the evaluation of drug effects on the ability to operate a motor vehicle in 2017 [38], although less detailed than other guidelines.

The aim of this article is to describe the methodologies used to investigate the effect of alcohol and drugs on the ability to drive safely, present the main advantages and challenges, and discuss disagreements between findings for some substances.

I. EXPERIMENTAL STUDIES

Experimental studies on the acute effects of alcohol and/or drugs on a person's ability to drive safely are performed by giving a defined amount of substance to a number of test persons and measure the effect on performance at pre-defined time points.

Participants are included in accordance with pre-defined specifications regarding age, sex, disease, current or previous substance use, and other issues. Studies in healthy volunteers serve as a good model to demonstrate principal drug effects on human performance, whereas patient studies in addition allow estimating the net effect of drug induced impairments and therapeutic benefits, e.g. symptom relief, on performance. Experimental studies can also take into account contributing factors that may affect drug effects on driving, such as age, gender, concomitant use of drugs and alcohol as well as duration of treatment.

Often, blood samples are taken to determine the drug concentration at the time of performing the tests to study whether there is a correlation between substance concentration and performance. Acute drug effects are often assessed around the time of maximal drug concentration (T_{max}) which is a time point when effects are most prominent [36]. However, assessments should also be repeated over a prolonged period to assess whether the relationship between effect and substance concentration in blood may change over time due to changed blood/brain substance concentration ratio and/or development of acute tolerance. Sub-acute effects may also be studied, such as residual effects (hangover) of hypnotics the morning after intake as well as withdrawal effects after long-term use. Ideally, participants should also receive multiple doses during several weeks of treatment to assess their influence on performance beyond acute use.

The optimal approach is to use a randomized double-blind study, where neither the researchers nor the participants are aware of the order of treatment conditions to which participants are randomized. A cross-over study design should be used, where each participant is tested with different doses of the test substance and placebo, and with a well-documented benchmark substance, such as alcohol.

When testing medicinal drugs, low to medium doses that fall within the therapeutic window are given acutely or sub-chronically. Ethical approval for studying large doses and chronic dosing is normally not given. It is also difficult to get ethical approval for studying illicit drugs. If approved, low to regular recreational doses are normally tested, and it is required that the test persons must have previous experience with the drug. For all substances, a risk assessment must be performed before submitting ethical committee and clinical trial applications.

The main advantage of experimental studies is that researchers have full control over substance dosing; they can compare different doses and different substances. Each study participant can perform different types of tests, and different types of subjects can be included. Well-documented tests on cognitive and psychomotor performance can be used. The studies can therefore easily be repeated in order to study the robustness of effects, study inter- and intra-subject variations, study sleep-deprived persons, or compare the effects of a drug alone with drug-alcohol or drug-drug combinations.

Experimental studies have other advantages as well. They only require small sample sizes to achieve sufficient statistical power to detect drug induced impairment. They can be used as part of drug development programs to predict driver impairment of novel compounds before

these enter the market. They also allow studying individual drugs rather than drug categories as is often the case in epidemiological studies.

The main limitations are: (1) that only low doses are tested, so the findings may not reflect real life situations of repeated intake, perhaps of large doses; (2) effects of any hangover and withdrawal symptoms after repeated abuse of large doses cannot easily be studied; (3) the participants know they are being tested; they may therefore act differently or over-achieve as compared to in a normal driving setting; (4) researchers have often neglected to include assessments that may indicate whether people actually want to drive when feeling "high" or impaired by the substance, or be extra careful if they decide to drive, or whether they prefer to avoid driving situations; and (5) the performed tests may not be relevant to skills necessary for safe driving and ability to drive in the traffic flow and react to emergency situations.

A potential problem is that the participating subjects may improve their performance over time due to repeated practicing in the behavioral tests performed after drug treatment. This learning over time may interfere and obscure effects of the substance being studied if the study design is not taking this into account. So, the participants must be sufficiently trained before the study starts to achieve a steady performance level. Placebo studies may also be performed throughout the study period to control for the potential obscuring effects due to learning, and treatment orders across subjects can be counterbalanced. Another potential challenge is that acute tolerance to the drug may be developed, causing less impairment at the same blood drug concentration after some hours. This must be taken into account when designing the study.

Experimental methods cannot be used to determine crash risk, only the degree of impairment of driving performance under somewhat artificial conditions, as well as cognitive, psychomotor and other mental functions related to driving caused by the given substance doses, or correlated with concentrations in blood at defined time points after substance intake. They can therefore only be used to determine whether a substance may reduce the ability to drive safely and whether this effect is related to drug dose or drug concentration in blood.

Many experimental studies have been performed for alcohol (see section IV A), and Strand and coworkers have summarized findings in studies of antidepressants, antihistamines, benzodiazepines and similar drugs, cannabis, GHB, ketamine, opioids, stimulants in a recent review article [146].

A. Controlled Laboratory Studies

These types of study are utilizing neurocognitive performance tests that are important for various aspects of the process of operating a car. Many skills that are needed to drive safely are tested. This may include attention, auditory and visual skills, cognitive performance, reaction time, motor coordination skills, vigilance, sedation, wakefulness, risk-taking or risk avoidance, aggression and psychotomimetic symptoms.

Many different functions should be tested in order to characterize the effects of the tested substance because different substances may affect different mental functions, and the tests may have different sensitivities for different substances. Testing should therefore be performed at three "Core Levels": Automative Behavior (well-learned, automatic action patterns), Control Behavior (controlled action patterns), and Executive Planning Behavior (general plans in interaction with ongoing traffic) [115, 164].

A number of validated computerized tests of basic psychomotor and cognitive functioning are available [159, 165]. An assessment of the sensitivity of different test assessing driving related skills to dose-related impairment by alcohol has been published by Jongen and coworkers [81].

B. Driving Simulator Studies

Driving simulators can be used to study psychomotor and cognitive functioning in a situation that is more similar to driving on the road [100]. It is then possible to study different types of driving situations, such as different road types, traffic densities, speed, day/night, different weather types, unexpected events, challenging situations, including situations where crash-involvement is likely to happen.

The main advantage is that driving tests can be systematically designed, presented and reproduced and that the performance is not associated with any driving risks.

A limitation is that the driving conditions are artificial, so the driver's response in a critical situation, e.g. when avoiding a crash, may be different in a simulator situation than when driving in actual road traffic. Moskowitz stated in 1985 that no simulator was capable of representing every aspect of the driving act simultaneously, but only a subset of them [105]. Even after technical improvements of the simulator technology, this might also be the situation at present, although to a lesser extent than in the earlier days of simulator studies.

Another challenge is that many drivers may experience simulator sickness, which may cause more careful driving [64]. It is, however, possible that simulator sickness can be reduced by repeated training sessions, as well as by drugs, complicating interpretation of the results. Simulators are also associated with higher levels of subjective and physiological sleepiness than real driving, which may hamper their comparability [53].

A validation study found that behavioral responses of sober drivers, as expressed by type and number of errors, were similar in a simulator and on-the-road driving [142]. Another study comparing a simulator study on the effects of alcohol with on-the-road driving found that the standard deviation of lateral position (SDLP) was largest when using a simulator; this may reflect a lack of perceived danger in the simulator and may therefore be more sensitive [63]. Others have, however, reported that the overall sensitivity of driving simulators to detect drug induced impairment was lower than on-the-road driving tests, particularly at low doses [81, 155].

C. On-The-Road Driving Studies

On-the-road driving tests are often considered as a "gold standard" for assessing driving impairment after using a psychoactive substance [121, 156, 157]. The primary test measure is SDLP, which quantifies the weaving while driving; this measure has been found to be more sensitive than other driving-related measures [62]. Studies may be performed on highways in actual traffic or in closed circuits. Specially equipped cars are used to measure the distance to the midline of the road or to a car in front. Lateral position, speed, distance between vehicles, and the use of accelerator and brake are recorded. In addition, it may be possible to record eye movements. There is always a licensed driving instructor present.

A limitation is that driving must be performed without challenging situations with increased risk for crash involvement; thus, the ability to avoid crash involvement cannot be studied.

Examples of measured performance in basic computerized tests and driving simulators or on-the-road driving are presented in Table 1.

Table 1. Examples of measured performance in experimental studies

Core level	Basic computerized tests	Simulator and on-the-road driving
Automative behavior	Tracking Alertness and vigilance	Tracking Performance over time Steering, weaving Vision
Control behavior	Response time (too fast/slow) Speed estimation Visual search Divided attention Psychomotor function	Distance to car in front Frequency of brake/accelerator use Reaction to stop signs Maneuvering during overtaking Divided attention
Executive planning behavior	Memory Planning skills Risk taking Impulsivity	Planning of driving route Speed choice Risk taking Hazard avoidance Inhibition of motor or cognitive responses Reaction to unexpected events

II. EPIDEMIOLOGICAL STUDIES

Analytical epidemiological studies involve comparing crash involvement among drivers who are using, versus not using, a substance that may potentially affect the ability to drive safely, or substance use among crash-involved versus non-involved drivers. This may include cohort, case-crossover, case-control, and responsibility studies [87]. It is more difficult to perform well-controlled epidemiological studies on the risk of crash involvement due to substance use than experimental studies on impairment after substance use. The main limitations are selection bias, information bias and confounding [49, 86]. Therefore, there are large variations in the risk estimates found in epidemiological studies.

Epidemiological studies are used to determine the crash risk posed by substance using drivers in real driving situations; not only the substance *per se*, as other factors than the substance itself are important, such as insight into own impairment, willingness to drive after substance use, and ability to compensate for impairment while driving.

Some large studies have also found significant associations between substances use and crash severity, or higher odds ratio for fatal crash than injurious crash [8, 11, 88, 143, 152], particularly for alcohol. This potential association should be kept in mind when comparing the findings in different studies, and when designing new studies.

Selection Bias

The studied drivers should constitute a random selection from the total population of drivers, but this is not always the case [87]. If participation is voluntary, the refusal rate may be higher among those who have used a psychoactive substance if they fear that it will be detected. Then, the prevalence of alcohol and drugs will be under-estimated. If data are based

on drivers selected by the police for toxicological investigation, such as crash-involved drivers, there may be a selection bias because drivers who appear unlikely to have used alcohol or drugs may less frequently be subject to alcohol and drug testing. Then, the prevalence of alcohol and drugs will be over-estimated. On the other hand, hit-and-run drivers cannot be included, resulting in likely under-estimation of alcohol and drug use.

It is therefore important to obtain very high participation rates; the best situation would be that non-participation is not allowed or could be excluded. High participation rates may be obtained if using data from road traffic registries combined with prescription data if the registries contain complete information.

Information bias

Information about substance exposure may be inaccurate or misinterpreted. If exposure data is based on self-reports, under-reporting is common [1, 89, 150], but over-reporting may also occur in some settings. If asked about substance use before being involved in a previous crash, the driver may incorrectly associate crash involvement with substance use due to inaccurate memory if this might be a plausible explanation for the crash.

If based on analytical testing of biological samples, the type of biological matrix and the cut-off concentration will affect the detection window after use, i.e. for how long time after last substance intake will the analytical finding be regarded as "positive" and thus indicate substance exposure. If only substance concentrations that may affect the ability to drive safely shall be studied, blood samples and appropriate cut-off concentrations must be used [44, 46, 158]. Misinterpretation of these issues may cause information bias.

For drivers injured in road traffic crashes, the blood sample for alcohol and drug testing may be taken several hours after the crash; the analytical results may therefore not always reflect the concentrations in blood at the time of the crash. This decrease of drug concentrations may be particularly fast for cocaine, gamma-hydroxybutyric acid (GHB) and tetrahydrocannabinol (THC) [22, 99, 166]. In studies of drivers injured or killed in crashes, findings of medicinal drugs may be a result of therapeutic administration after the crash during emergency care or resuscitation efforts; those findings must be excluded from the dataset. Analysis of post-mortem blood samples may not reflect the alcohol and drug concentrations in blood at the time of death due to postmortem changes [32, 54, 118].

There may also be information bias regarding crash involvement if data is based on self-reports.

Covariates and Confounding

Several factors may be related both to substance use and crash involvement, such as age, sex, time of day, day of the week, and driving experience. Also impulsivity, sensation-seeking behavior, as well as subjective norms may predict alcohol and drug use and driving behaviors. Other factors that may modulate the risk of crash involvement after using a psychoactive substance are driving experience, whether or not the driver has passengers and whether passengers are impaired by alcohol or drugs, road traffic speed, weather conditions, exhaustion or sleepiness, and diseases. Some of the covariates may be difficult or practically impossible to include in statistical evaluation of findings.

A. Pharmacoepidemiological Cohort Studies

Cohort studies on substance use and crash involvement are studies investigating two groups with different substance exposure. In most cases, a substance exposed cohort is composed by drivers who are using a medicinal drug, while an unexposed cohort is composed by drivers who are not taking the drug in question. The numbers of crashes in those two

cohorts are recorded and the standardized incidence rate for crash involvement is calculated. Some studies use a case-control design instead and calculate the odds ratio for crash involvement. Significant covariates such as age, sex, driving experience, and annual driving distance may be adjusted for in the statistical evaluation of data. If relatively more crashes have occurred among drivers using the drug than among non-drug using drivers when adjusted for confounders, an association between the drug and crash involvement may be found.

Drug exposure is in most studies based on records in prescription registries, whereas crash involvements are found in road traffic crash databases, hospital or police records, or insurance databases. Information about drug use and crash involvement may also be based on self-reports.

The main strengths of cohort studies are that drivers in actual road traffic are studied, many hundred thousand drivers may be included when using large databases, and crash risk associated with prescription of medicinal drugs may be calculated.

One major limitation is that comprehensive and accurate data are required and that coupling of information for individuals can be done. Road traffic crashes are recorded only if detected and reported by the police or insurance companies, depending on regional legislation and routines, and may therefore be inaccurate. Another major limitation is that actual drug use is not recorded, only that the prescription had been given, or that the drug has been dispensed at a pharmacy, or that the participant reports use. In addition, there is no recorded information on whether the taken dose is according to the prescription and whether alcohol or other drugs are taken in addition to, or instead of, the prescribed drug. It is also difficult to distinguish between crashes related to drug use and those related to the disease that is being treated, i.e., confounding by indication bias [144].

Another limitation is that driving patterns, including the weekly driving distance, may be different among drug users than other drivers. The drivers may choose not to drive as frequently as before when taking medication, and the need for driving may be significantly reduced if they are on sick leave.

A third limitation is that cohort studies of this type are using data on crash involvement, not crash responsibility.

Cohort studies based on prescription and road traffic crash registries have been performed for benzodiazepines and similar substances, opioids, and some other medicinal drugs, whereas studies on cannabis have been based on self-reported data; see the review article by Gjerde et al. [45].

B. Case-Crossover Studies

A special type of pharmacoepidemiological cohort studies is the case-crossover design, which examines the crash rate in a cohort of drivers who have received a prescription drug. The standardized incidence rate for crash involvement is calculated for the first weeks after the drug has been dispensed at a pharmacy and compared with periods where the drug is not used. Thus, the cases (i.e. drivers who are taking the drug) can be their own controls (i.e. when the drivers are not taking the drug). Thereby, a number of confounders can be eliminated, such as age, sex, driving experience, traffic safety attitudes, and personality. However, it may still be difficult to distinguish between increased crash risk due to disease itself or due to medication to treat the disease. Studies based on prescription and crash registries have been performed for antidepressants, benzodiazepines, opioids and some other medicinal drugs [45].

Case-crossover studies may also be performed based on self-reported data [4].

C. Case-Control Studies

Case-control studies are often regarded as theoretically the best epidemiological method to calculate the association between an exposure and an outcome [9, 67, 136]. In our setting, the exposure (independent variable) is substance use, whereas the outcome (dependent variable) is crash involvement. Cases are drivers involved in crashes, whereas controls are drivers stopped at random in road traffic. Substance use is determined by analysis of oral fluid, blood or urine samples, or by self-report. Cases are most often selected from hospital emergency rooms or autopsy databases, whereas controls are most often selected in roadside surveys, most often in collaboration with the police. The risk for crash involvement associated with substance use is calculated as odds ratio.

The main strength of case-control studies of this type is that actual drivers in normal road traffic are being studied, both therapeutic and recreational use and misuse are included, the studies require lower numbers of participants than cohort studies, and the actual crash risk associated with the use of psychoactive substances can be estimated.

It is, however, very difficult to perform good studies on substance use and crash risk using a case-control approach, mainly because it is almost impossible to avoid serious selection bias [44, 87]. Information bias is also a frequently encountered error, particularly misclassification of substance use, or defining substance exposure differently for cases than for controls [44, 49]. Substance concentrations are mostly re-coded as positive or negative. However, the median substance concentration may be very much different among substance-positive drivers defined as cases compared to the controls, even when the same cut-off concentrations are used. This may cause a significant information bias. Case-control studies also require fairly large samples sizes to achieve sufficient statistical power because prevalence of drug use among cases and controls are generally quite low.

Also confounding factors make interpretation of findings difficult [44]. To avoid the most serious errors related to confounders, the data should at least be adjusted for age and gender and time and day of week, as those factors are among the most important confounders. Other confounders may also significantly affect the estimation of the crash risk associated with substance use (see the section on Covariates and Confounding above).

The crash-involved drivers who are included as cases in the studies are not always responsible for the crash. It is expected that the odds ratio for crash involvement will be higher if only crash responsible drivers are included and drivers who are not responsible are excluded.

A number of case-control studies on the association between use of alcohol or drugs with crash involvement have been published; see the review by Gjerde et al. [45].

D. Responsibility Studies

Responsibility studies (also called culpability studies) constitute a subtype of the case-control study design [87, 130, 134]. Drivers identified as being partly or mainly responsible for a road traffic crash are selected as cases, and drivers who are involved in crashes but not responsible are selected as controls, assuming that they constitute a random selection from the driving population. The incidence of substance exposure among drivers who are responsible for crashes is compared to those who are not responsible. The association between being responsible for a crash (as dependent variable) and alcohol or drug exposure (as independent variables) are calculated as odds ratios.

The main strength is that blood samples are normally collected from both responsible and non-responsible drivers; then, substance exposure can be defined equally among both cases and controls. Other strengths are that real drivers in normal road traffic are studied, and that

substance concentrations reflect actual substance use in the studied population, both therapeutic and recreational use and misuse.

The main limitation is that it may be difficult to determine responsibility in an un-biased way and that a driver who is deemed not responsible may have some partial responsibility, as the driver was unable to avoid the crash. The crash risk estimates may therefore differ from "standard" case-control studies, as it is likely that the non-responsible driver may not represent a random selection of drivers from normal road traffic, and cases are not merely crash-involved drivers, but crash-responsible. Another likely bias is that substance concentrations may not reflect the concentrations at the time of crash. They are in most studies reported as negative/positive; differences in median substance concentrations between cases and controls can then not be taken into account, which may cause a significant information bias.

Very few studies have investigated acute substance intoxication; most studies have defined substance exposure as detecting traces of the used substance in blood samples by using low concentration cut-offs that may detect substance intake several hours or days later.

A number of responsibility studies have been published, see previously published reviews [45, 134]; some studies were based on recorded unsafe driving actions as a proxy for crash responsibility.

E. Meta-analyses and Systematic Reviews

A number of meta-analyses on the association between substance use and road traffic crashes have been published. In those reports, data from many independent studies have been combined. The validity of the meta-analyses depends on the quality of the selected independent studies as well as the overall evaluation. The same applies to systematic reviews.

Knowledge about pharmacology, epidemiology, statistics and traffic safety research is needed in order to prepare meta-analyses and systematic reviews of good quality. In general, some published meta-analyses and systematic reviews may suffer from lack of insight into one or more of those scientific fields, being unable to exclude studies of poor quality or misunderstand the findings [71]. One example is that the authors may not understand whether substance exposure is defined as substance-induced impairment or merely detection of traces of substance in biological samples, reflecting intake during the last days, such as in a recent meta-analysis of studies on acute cannabis intoxication [42, 132]. Sometimes, data from studies based on urine testing, blood sample testing and self-reports are mixed into the same meta-analysis. Therefore, the conclusions in some meta-analyses and systematic reviews may be inaccurate.

III. REAL-CASE STUDIES

Real-case studies are descriptive studies of drug-impaired drivers. This may be DUI offenders apprehended by the police or involved in road traffic crashes. In contrast to analytical epidemiological studies, the drivers are normally not compared with a reference (control) group.

A. Drivers Arrested for Driving Under the Influence

Cross-sectional studies of drivers arrested by the police suspected for DUI of alcohol or drugs shows which substances are most commonly used by those who are apprehended as well as substance concentrations and multi-substance use. Most DUI offenders are arrested due to dangerous or aberrant driving, such as weaving, speeding, not stopping for red light or

stop sign, or crash involvement; relatively few are arrested in random roadside police controls or controls at sobriety check-points. There is thus a marked selection bias, where the risk for apprehension is highest for those who are most significantly impaired or intoxicated.

Repeated studies of this type may show trends in substance use among apprehended DUI offenders over time, including changes in substances used for different age groups and sex.

Data on substance type and concentrations in blood may also be compared with observations of unsafe driving actions to characterize the type of impairment that is caused by different substance types, such as alcohol, other depressants, stimulants, hallucinogens, and cannabis.

Drivers suspected for DUI are in many countries also examined using standardized clinical tests for impairment or field sobriety tests. If these tests are performed in connection with collection of a blood sample, the relationship between substance concentrations and degree of impairment may be assessed. This type of study is sometimes called "semi-experimental", as the participants are drivers who have taken substance dose(s) that are "normal" for them, but not controlled by the researchers, whereas the clinical examination comprises standardized psychomotor and cognitive tests.

The main advantage is that the substance concentrations in blood are often very much higher than those used in experimental studies. Since the researchers do not give any substance to the participants, ethical approval for such high-dose studies is not needed. The fact that the participants are actual substance users, not healthy volunteers, may also be regarded as an advantage. The results show the wide range of substance concentrations that may be associated with clinical impairment: low concentrations may be found among impaired drivers with low tolerance to the substance and high concentrations may reflect high tolerance if the clinical impairment is low to moderate. Studies of this type may also indicate whether there is an overall positive correlation between substance concentration and degree of impairment.

The main limitation is a selection bias as the included drivers are stopped by the police based on dangerous or aberrant driving. Therefore, it is not possible to determine an unbiased correlation between substance concentration in blood and results of field sobriety tests or clinical tests of impairment. Another limitation is that data on the amount of substance taken, information about the time and frequency of use, and whether it was for taken for therapeutic or recreational purposes, has in most studied not be collected because the data were based on standardized questionnaires used by the police.

Semi-experimental studies of this type have been performed for alcohol, amphetamines, benzodiazepines and similar medicinal drugs, cannabis, and opioids; see review by Strand et al. [146].

B. Drivers Involved in Road Traffic Crashes

Cross-sectional studies of drivers involved in crashes can be used to determine the prevalence of different psychoactive substances as well as substance concentrations. These studies may be used to compare substance use among different groups, e.g. drivers arrested for DUI, drivers involved in fatal versus non-injurious crashes, or car drivers versus motorcycle riders. Substance use among sub-groups can be studied, e.g. sex, age groups or drivers involved in single-vehicle crashes, and changes in substance use over time can be monitored.

Comparison between different countries or regions may be difficult if studies are not harmonized regarding type of biological sample, types of substances, as well as detection limits or cut-off concentrations if analyzing biological samples. This has so far been done in

few studies [94, 95, 110]. The same applies when monitoring changes over time in a country or region.

The risks for crash involvement cannot be calculated based on studies of this type. However, findings may be used to hypothesize which substances may cause impairment and thus increase the crash risk, and at which concentrations.

IV. AGREEMENTS AND DISAGREEMENTS BETWEEN STUDIES

Neither experimental, epidemiological nor real-case studies can alone provide sufficient documentation and understanding about the risks for crash involvement after using a psychoactive substance. All methods have distinct advantages and limitations. Therefore, those methodologies may in some instances apparently provide conflicting data. However, the combination of the three methods may be used to create a broader and more complete picture as they may complement each other when assessing the effects of substance use on road traffic safety.

Experimental studies indicate which substances and at which doses and concentrations the ability to drive safely may be affected. Real case studies indicate which substances are found in drivers involved in crashes, or among arrested DUI offenders as proxy for crash involvement, and at which concentrations. Well-designed epidemiological studies (cohort-, case-crossover-, case-control- and culpability-studies) may be used to estimate the actual crash risk posed by drivers using different psychoactive substances, and compare the risks posed by users of cannabis, stimulants, hallucinogens, and depressants of different types.

To illustrate some similarities and disagreements for the three methodologies, we have presented data from a selection of representative studies of alcohol, amphetamine/methamphetamine, cannabis, and diazepam below.

A. Alcohol

1. Experimental Studies

The first experimental studies of alcohol-related impairment were performed in the early 20th century. Studies included the effect of alcohol on typewriting efficiency [60] and studies on response time between stop signaling and actual application of brakes while driving [61]. The effect of alcohol on cognitive and psychomotor functions has later been studied in a number of computer-based studies of mental and psychomotor functioning, in driver simulators, and on-the-road driving studies, and several review articles have summarized the findings [72, 80, 81, 107, 135]. Due to the clear and well-documented relationship between BAC and impairment, alcohol is often used as a benchmark standard when studying other substances.

The Norwegian researcher Klaus Hansen performed a number of semi-experimental studies on the degree of impairment in relation to the BAC among drivers during 1915-1937; the documentation was used to set the legal BAC limit for DUI of alcohol in Norway, as the first country in the world, to 0.05% in 1936 [55, 56].

2. Epidemiological Studies

Holocomb published the results of an analytical epidemiological study on alcohol and crash involvement in 1938, comparing the prevalence of alcohol and the BAC in random drivers and crash-involved drivers in a case-control study [65]. The results indicated that crash risk increased with higher BAC. The first large-scale study was performed by

Borkenstein and coworkers in 1962-63 [15]; they found that a BAC above 0.04% was associated with increased crash rate and that the risk increased with increasing BAC. Later studies have confirmed the findings [12, 90, 138, 148, 161, 168]. However, the estimated odds ratio for crash involvement at a defined BAC has not been the same in different studies, indicating that the BAC alone cannot fully explain the crash risk [40]. It is likely that confounders related to personality, risk perception and social norms may also play a role. Also differences in study protocols, execution and statistical evaluations may cause variation in risk estimates.

3. Real-Case Studies

In the first published study of alcohol use among crash-involved drivers, which was published in 1904, found that in 19 out of 25 fatal crashes, the drivers had used alcohol during the last hour before the crash [34]. A study of 119 drivers published in 1934 found that the majority had been drinking [60]. Since then, many studies have confirmed the large proportion of alcohol-related crashes [47].

The proportion of BAC above 0.08% among drivers killed in crashes in the USA declined from 49% in 1982 to 31% in 2011 [37] and 28% in 2016 [111]. In Sweden, 22% of drivers killed in crashes during 2008-11 had BAC > 0.02% with a mean BAC of 0.172% [2]. In Norway, 25.3% of drivers killed in crashes during 2001-10 who were investigated for alcohol use had BAC > 0.02%, 20.6% had BAC > 0.1% [19]. The mean BAC of drivers killed during 2005-15 was 0.16% (Anja Valen, Oslo University Hospital; personal communication).

4. Agreements Between Studies

Experimental and epidemiological studies confirm the association between increasing BAC and increasing impairment and crash risk. Real-case studies show that DUI of alcohol is a contributing factor in a large proportion of crashes. There is no significant disagreement between findings in different types of studies. However, experimental methods seem more sensitive to the effects of alcohol, showing impairment of some skills at BAC of 0.02% or lower [106], whereas epidemiological studies have documented increased crash risk at BAC of 0.02-0.04% and higher [15, 135, 161].

B. Amphetamine and Methamphetamine

1. Experimental Studies

Experimental studies of cognitive and psychomotor performance have been performed by acute administration of amphetamine or methamphetamine in doses of 10-40 mg to healthy volunteers, giving mean concentration in blood of about 50-100 ng/mL after 3-4 hours. Overall, the studies found neutral or stimulatory effects when given alone, and stimulatory effects were not strong enough to counteract the impairing effects of alcohol or sleep [124]. Some studies found enhancement of functions in fatigued and sleep-deprived persons, others found a small decrease in overall driving performance in a simulator after amphetamine administration at the same dosing [7, 146].

A driving simulator study with 39 participants who were weekly users of methamphetamine and a control group of non-users was performed in Australia [16]. The methamphetamine users were significantly more likely to speed and to swerve from side to side when driving. They also left less distance between their vehicle and oncoming vehicles when making a right-hand turn. There were higher levels of impulsivity and antisocial personality disorder in the methamphetamine-using cohort.

2. Epidemiological Studies

In epidemiological studies, significant associations between use of amphetamine/methamphetamine and crash involvement were found in most studies, whereas a few studies did not find significant associations [45, 59]. Most of the studies were performed by using a classical case-control design whereas a few used responsibility design. The largest case-control study of alcohol, drugs and crash involvement performed so far, the European DRUID Project (Driving under the Influence of Drugs, Alcohol and Medicines) [138], included 2490 seriously injured drivers, 1112 fatally injured drivers, and more than 36,000 drivers in random road traffic as controls; the adjusted odds ratio for serious injury in road traffic crashes associated with amphetamines was 14.2 (95% CI 5.8-34.4), whereas the adjusted odds ratio for fatal injury was 34.3 (95% CI 13.2-89.5) [11].

Common challenges with case-control studies are selection bias, information bias, and confounding [44]. We therefore expect that the calculated odds ratios are inaccurate, in most studies over-estimated.

A study on the odds ratio for being arrested for DUI was higher for amphetamine/methamphetamine using drivers than for those who had used other drugs [13].

3. Real-Case Studies

The prevalence of amphetamine or methamphetamine in blood samples from drivers arrested for DUI varies a lot between different countries; the prevalence is particularly high in some northern European countries and Australia [47]. In Sweden, amphetamine was detected in 60% of blood samples taken from drivers suspected for DUI of drugs in the period 2000-2004 [78]. In Norway, amphetamine was detected in 27.6% and methamphetamine in 13.4% of suspected drug-impaired drivers arrested during 1990-2015 [154], in Germany amphetamine, methamphetamine, MDMA or MDEA was found in 21.1% of arrested drug drivers [108]. On the other hand, a Swiss study found methamphetamine to be present in only 3.6% of blood/urine samples from drivers suspected for DUI of drugs [5].

The concentrations of amphetamine in drivers arrested for DUI are often very high. The reported mean concentration in blood samples from arrested impaired drivers in Sweden with amphetamine as the only drug (n = 33,642) was 800 ng/mL [75]. The mean concentration among arrested drivers in Norway during 1990-2015 (n=30,968, cut-off 40 ng/mL) was 380 ng/mL; for methamphetamine (n=15,039, cut-off 45 ng/mL) the mean concentration was 450 ng/mL (Anja Valen, Oslo University Hospital; personal communication). A large proportion of the arrested amphetamine-impaired drivers are chronic long-term users of the drug, many take it intravenously at very high doses [75]. A Swedish study found that 75% of drivers killed in road traffic crashes who tested positive for amphetamines had been arrested previously for use of illicit drugs or DUI [76], confirming problematic drug use.

In a study of arrested DUI offenders in Germany where amphetamines were the only psychoactive substance found, the mean amphetamine concentration in plasma was 181 ng/mL [108], which is lower than averages found in Scandinavian studies.

Among 1375 drivers/riders killed in crashes in Western Australia during 2000-2012, methamphetamine was found in 7.4% [116]. In Norway, 9.0% of 676 investigated drivers and 6.3% of 207 motorcycle riders killed in crashes during 2001-2010 tested positive for amphetamine/methamphetamine [19, 20]. In Sweden, 3.4% of 895 drivers tested positive for amphetamines in 2008-11 [2].

The mean concentration of amphetamines in killed drivers in Sweden during 2008-11 (n=30) was 1030 ng/mL [2]. The mean concentration in blood samples from car drivers killed in road traffic crashes in Norway during 2005-13 was for amphetamine 900 ng/mL (n=29) and methamphetamine 1070 ng/mL (n=23) (Anja Valen, Oslo University Hospital; personal communication).

Clinical tests of impairment of arrested DUI offenders who tested positive for only amphetamine found that almost 60% of apprehended drivers with amphetamine concentrations in blood of 40-100 ng/mL were judged clinically impaired, while about 70% of those with amphetamine concentrations above 270 ng/mL were judged impaired. Younger drivers were more often judged impaired than older drivers at similar concentrations [51]. A Swedish study was not able to find an association between concentration and impairment; however, the statistical power was low [73].

Case studies of arrested amphetamine impaired drivers indicated that they had been apprehended due to aberrant or dangerous driving, such as changing lane rapidly without signaling, tailgating the car ahead, speeding, and weaving [96, 102]. Studies of arrested DUI offenders found that those who had used stimulants had difficulties when performing balance tests, walk-and-turn, and finger-nose-test [96, 119].

Amphetamine and methamphetamine can be taken orally, snorted, or injected; the effects are then similar for the two substances. Methamphetamine can also be smoked as "crystal meth". The effects of amphetamine and methamphetamine on behavior and crash risk are mostly related to dose and frequency of use, but the way of administration may also have some modulating effect.

4. Disagreements Between Studies

Experimental studies with amphetamine and methamphetamine have often showed improvement in skills related to driving or fail to find any effects at all. Most epidemiological studies, however, found that stimulant use increased the crash risk.

Experimental studies of amphetamines have mostly been performed by administration of a single, small dose to healthy volunteers, normally about 10-40 mg, giving peak plasma concentration of about 140 ng/mL [146]. Patients using amphetamine or methamphetamine for therapeutic purposes may have peak plasma concentrations of 200 ng/mL or lower [137, 139]. It is unlikely that therapeutic use of amphetamines may significantly reduce the ability to drive safely.

The concentrations of amphetamines in most arrested or crash-involved drivers are higher, because most of them are abusers who take 50-300 mg in each dose, several times a day and for many days in a row, as described above. As a result of the large doses for extended periods of time, irrational behavior may occur, as well as fatigue, paranoia and psychotomimetic symptoms [24, 101, 117]. It is likely that the observed increase in crash risk associated with amphetamines may be related to those effects, as very high amphetamine concentrations in blood are often found in crash-involved drivers and arrested DUI offenders [75, 102]. However, also therapeutic amphetamine concentrations in blood are sometimes found in clinical impaired DUI offenders, suggesting that those drivers may be on a declining concentration curve after taking larger doses.

Based on the data presented above, the differences between findings in experimental studies and epidemiological studies on the association between amphetamines and the ability to drive safely are therefore most likely related to dose and frequency of use [101].

C. Cannabis

1. Experimental Studies

A large number of studies have found that cannabis causes a dose-related mild to moderate impairment in neurocognitive and neurophysiological functions that may reduce the ability to drive safely, and several review articles have been published [14, 57, 122, 146]. Ramaekers et al. reported in a review that the degree of performance impairment observed in experimental studies after smoking doses up to 300 µg/kg THC were equivalent to the

impairing effect of an alcohol dose producing a BAC ≥0.05% [122], this corresponds to an average peak THC concentration in serum of 7-10 ng/mL [50]; about 3-5 ng/mL in whole blood. Smaller performance impairments, however, have been demonstrated to arise at THC levels > 2 ng/mL in serum [125].

The results of several studies indicate that highest degree of impairment appear later than the peak THC concentration in blood after smoking cannabis. A counterclockwise hysteresis relationship has been demonstrated several times [23, 68, 113, 140]. However, it has also been shown that a strong relationship between performance impairment and THC concentrations in blood can be demonstrated if the magnitude of cannabis induced impairment is discarded. For example Ramaekers et al. [122] and Grotenhermen et al. [50] determined the relationship between THC concentration in blood and a binary representation of impairment (i.e. present or absent). Ramaekers et al. [122] demonstrated that the number of psychomotor observations showing impairment significantly increased as a function of THC in serum. Likewise, Grotenhermen et al. [50] showed that the number of psychomotor tests showing cannabis impairment increased as a function of THC concentration in serum.

Experimental studies have demonstrated that levels of cannabis induced impairments may differ as a function of cannabis use history. Impairment levels are maximal in occasional cannabis and less or even absent in frequent or daily users due to tolerance [28, 123]. It is unknown, at present, at which cannabis use frequency tolerance becomes complete, if ever [126, 127].

2. Epidemiological Studies

Studies on the association between cannabis use and crash risk have been performed using cohort, case-crossover, case-control, and responsibility designs. Most studies found significant association between cannabis use and crash involvement or crash responsibility. However, the odds ratios were lower than for alcohol or amphetamines, in most studies less than 3.0 [3, 45, 57, 98]. Røgeberg and Elvik [132, 133] attempted to re-calculate the odds ratios in a meta-analysis of many previous studies to eliminate an upward bias in odds ratio estimations. The re-calculations indicated a statistically significant risk increase of low-to-moderate magnitude [random-effects model odds ratio 1.32 (95% CI 1.09–1.59), meta-regression odds ratio 1.18 (95% CI 1.07–1.3)]. The included data were based on studies using low cut-off concentrations for THC in blood, or studies based on urine testing, and did therefore not specifically address the risk during acute cannabis intoxication [42]. It is therefore likely that only a small proportion of those who were categorized as cannabis-exposed were actually intoxicated or “high” in the included studies, thus underestimating the risk posed by driving while intoxicated by cannabis. Røgeberg has also performed a meta-analysis of culpability studies on cannabis use and crash responsibility avoiding interpretational bias, estimating a crash risk of 1.42 (95% CI 1.16-1.40) [131].

The risk associated with likely acute cannabis intoxication, defined as a THC concentration in whole blood ≥ 5 ng/mL, has been studied in few investigations. Using the responsibility study design, estimated odds ratios for crash responsibility were 1.0 (95% CI 0.4-2.4), 2.1 (95% CI 1.3-3.4) and 6.6 (95% CI 1.5-28) [31, 92, 120], whereas a case-control study found an odds ratio for crash involvement of 14.3 (95% CI 2.0-101.1) [91]. The main problems with those studies were low statistical power, possibly information bias as the THC concentration in the analyzed blood samples might not represent the concentration at the time of crash, and a likely selection bias for the case-control study as the participation rate was low.

3. Real Case Studies

Cannabis is the most common non-alcohol drug detected in blood samples from suspected drug-impaired drivers in many countries [47]. In Norway, THC was found in 23% of the analyzed blood samples in 2000, increasing to 34% in 2015 [153]; similarly, the proportion testing positive for THC increased from 18% in 1995 to 30% in 2003 in Sweden [77].

The main reasons for being apprehended for DUI of cannabis was in a Californian study found to be speeding, unable to maintain lane position, ran red light or stop sign, unsafe lane change, collision, going too slow, no headlights at night, no turn signals, and driving the wrong way [26]. Drug recognition expert examination characteristics of cannabis-impaired drivers found that the strongest indicators were walk and turn problems, one leg stand sway, finger to nose misses, as well as eyelid tremors, blood shot eyes, and pupil rebound dilation; the speech was also often affected [26, 27, 58].

A study of drivers arrested for drug-impaired driving in San Francisco, CA, found the mean THC concentration in blood was 4.9 ng/mL; among those who tested positive only for THC, the mean concentration was 5.8 ng/mL. Among drivers killed in crashes, the THC concentrations were higher (mean 11.7 ng/mL, 20.3 ng/mL among cannabis-only drivers) [97].

The prevalence of THC in biological samples from drivers killed in road traffic crashes varies between different countries or states and has changed over time [21, 47]. Norwegian studies found THC in blood samples from 7.2% of car and van driver killed in road traffic crashes during 2001-2010 [19] and 4.3% among killed motorcycle riders [20]. A study of crash data from six American states found that the proportion of killed drivers who tested positive for cannabis increased from 4.2% in 1999 to 12.2% in 2010 [17]. A study in Washington state estimated an increase in THC detections among killed drivers from 8.5% in 2010 to 17.0% in 2014 [147]; it is likely that this increase was related to the legalization of recreational cannabis use in December 2012. Among fatally injured drivers in Canada who were tested for drugs, the proportion who tested positive for cannabis increased from 15.9% in 2000 to 20.9% in 2015 [151]; however, the proportion who was tested for drugs increased during this period, so the data should be interpreted with caution. The 2018 Canadian Cannabis Survey found that among those who had used cannabis during the past 12 months, 39% reported that they had ever driven within two hours of using cannabis [48]. It is likely that the number of drivers testing positive for cannabis will increase further after legalization for recreational use in Canada.

4. Disagreements Between Studies

The results from different types of studies show apparently different findings regarding the risk posed by cannabis in road traffic: experimental studies and real-case studies found significant impairment of mental and psychomotor functions, whereas epidemiological studies found a fairly low but statistically significant increase in crash risk.

There may be several reasons for the differences. First of all, it is very difficult to study the effect of acute cannabis intoxication in epidemiological studies. No study has been able to determine the THC concentration in crash-involved drivers immediately after the crash; by the time samples were taken, the THC concentrations had declined significantly. The THC concentration in blood may stay detectable but low for a very long time after use, depending on inter-individual differences as well as frequency of cannabis use. Often, THC concentrations in blood above 1 ng/mL have been regarded as proof of cannabis exposure, but cannabis use may for the vast majority of those drivers have occurred several hours ago, or perhaps more than one day ago. So, most epidemiological studies have not been able to distinguish between acute intoxication and previous cannabis use, or occasional and daily

users, which may bias the study findings. Other difficulties are related to selection bias and confounding.

Investigators have reported that some cannabis users are aware of their impairment and may try to be more cautious by driving more slowly and avoid taking risks if deciding to drive while "high" [103, 129]. However, studies have found that drivers under the influence of cannabis were not able to compensate for weaving, speedometer monitoring, had increased decision and response times, and difficulties in handling unexpected events [57, 141]. How much this attempted compensation reduces the crash risk is therefore not clear.

D. Diazepam

1. Experimental Studies

Early studies on diazepam performed in the 1960-70s found that diazepam could reduce both mental and psychomotor functions that are important for safe driving [52, 83, 93, 109]. Since then, a large number of studies have been performed. A meta-analysis of 103 experimental studies of diazepam was performed by Berghaus and co-workers as part of the DRUID Project [10]. The degree of impairment after single administration of 5-20 mg diazepam to healthy individuals was summarized, as well as studies of repeated use among patients. There was a linear correlation between drug concentrations in plasma and performance impairment. Berghaus et al. estimated that a diazepam concentration in plasma of 320 ng/mL produced the same degree of impairment as a BAC of 0.05% [10], whereas Vindenes et al. estimated that impairment similar to BAC of 0.05% was obtained at a diazepam concentration of 143 ng/mL in whole blood [160] (the blood/plasma concentration ratio for diazepam is about 0.55 [79, 104]).

2. Epidemiological Studies

Most epidemiological studies have investigated benzodiazepines as a drug group, not individual substances and several reviews and meta-analyses have been published [25, 35, 45, 114, 145]. Statistically significant associations have been found between use of benzodiazepines, including diazepam, and crash involvement.

Among the studies that specifically addressed diazepam, investigations of crash involvement among patients using diazepam found an incidence rate ratio of 1.93 (95% CI 1.54-2.43) during the four first weeks of use [39] and standardized incidence rates of 2.8 (95% CI 2.2-3.6) during the first week after dispensed from a pharmacy [18], and 3.1 (95% CI 1.4-6.5) during the first four weeks in another study [112]. A study of elderly drivers found a relative risk for injurious crash of 2.4 (95% CI 1.3-4.4) for ≥20 mg diazepam per day [128].

Case-control studies found odds ratios for crash involvement associated with diazepam of 0.9 (0.1-7.0) [43] and 6.4 (2.5-16.7) [41]. Similar odds ratios have been found in studies of the benzodiazepine drug group in total; see e.g. reviews by Elvik [35] or Dassanyake et al. [25]. The risk for crash involvement after using benzodiazepines is lower than the average risk associated with alcohol use; the DRUID Project found for alcohol an overall adjusted odds ratio for being seriously injured of 9.8 (95% CI 8.2-11.7), and for being fatally injured of 19.0 (95% CI 14.4-25.0), whereas the odds ratios associated with the use of benzodiazepines or Z-drugs were 1.8 (95% CI 1.2-2.7) for being seriously injured and 4.6 (95% CI 3.3-6.4) for being killed [11].

Other studies have found a positive correlation between daily dose of benzodiazepines and crash risk [6, 128].

3. Real Case Studies

The use of diazepam in Norway is fairly high compared to many other countries. During 1990-2015, an average 15% of drivers suspected for drug impaired driving in Norway tested positive for diazepam in concentrations above 142 ng/mL in whole blood [154], which was the maximum analytical cutoff used during the study period. About 80% of those tested also positive for one or more other drugs; the median diazepam concentration was 340 ng/mL and 7% had concentrations above 1100 ng/mL (Anja Valen, Oslo University Hospital; personal communication), corresponding to 2000 ng/mL plasma [79, 104]; a concentration that may be regarded as the upper concentration limit of therapeutic use [137].

Among car and van drivers killed in road traffic crashes in Norway during 2001-10, 5.5% tested positive for diazepam [19].

Studies of suspected DUI offenders and fatally injured drivers in several other countries also found high prevalence of benzodiazepines, but the types of benzodiazepines as well as the prevalence in blood samples differed between countries [94, 149].

4. Agreements Between Studies

Results from experimental and epidemiological studies indicate that the use of diazepam may impair the ability to drive safely and increase the crash risk [10, 45, 146]. The risk is related to the daily dose [6, 128], but development of tolerance may reduce the risk [30]. Studies on the prevalence of diazepam among arrested DUI offenders and crash-involved drivers also indicate that impaired driving may be caused by diazepam, particularly when taken in large doses.

CONCLUSIONS

Experimental, epidemiological and real-case studies have different advantages and limitations when used to study the effect of substance use on the risk for involvement in a road traffic crash. All types of studies are needed to assess the impact of the use of different psychoactive substances on road traffic safety. For some drugs, such as cannabis and stimulants, the results of experimental studies are not always in line with those of epidemiological studies. Those disagreements may be caused by limitations in study designs and in interpretation of findings. For example, many drug-impaired drivers are multi-substance users that combine high doses of illicit, prescription drugs and alcohol. Such real-life incidences cannot be mimicked in experimental studies due to ethical constraints.

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