European Monitoring Centre
for Drugs and Drug Addiction

INSIGHTS EN

ISSN 2314-9264

Drug use, impaired driving and traffic accidents

Second edition

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for Drugs and Drug Addiction

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Cataloguing data can be found at the end of this publication.
Luxembourg: Publications Office of the European Union, 2014
ISBN: 978-92-9168-687-2
doi:10.2810/26821

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Printed in Spain

Printed on elemental chlorine-free bleached paper (ECF)

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Foreword

The mobility provided by road transport, particularly the car, allows many Europeans to enjoy a lifestyle characterised by flexibility and independence. However, if we count the lives lost and injuries inflicted as a result of road traffic accidents, it is clear that these benefits come at a price: the most recent statistics reveal that more than 28 000 people die on European roads each year, while a further 1.34 million are injured.

In 2003, the European Union's third Road Safety Action Programme set the ambitious target of halving the number of road deaths in the European Union in 2010. For the now 28 Member States of the Union, this would amount to approximately 27 500 lives lost on the roads.

Many of the accidents and deaths that occur on European roads are caused by drivers whose performance is impaired by a psychoactive substance (alcohol, illicit drugs, psychoactive medicines or a combination of these substances). In order to meet the 2003 Action Programme's target of a significant reduction in fatalities in road traffic, it was necessary to address risks associated with all components of the road transport system, including driver performance. While public concerns with regard to illicit drugs and medicines in traffic were growing, knowledge at that point was insufficient to address these concerns.

When the 2003 Action Programme was introduced, it was estimated that about 25 % of fatalities on European roads were the result of the influence of alcohol, but a lack of comparable studies meant that the proportion due to the effects of illicit drugs or psychoactive medicines was unknown. For this reason, the DRUID (Driving Under the Influence of Drugs, Alcohol and Medicines) project was established, with the aim of estimating the size of the problem and examining the range of countermeasures. The DRUID project — part of the 6th Framework Programme — was established in October 2006, ran for 5 years and involved 38 consortium partners from 17 EU Member States and Norway. The overall objective of the DRUID project was to provide scientific support to EU road safety policymakers by making science-based recommendations concerning responding to driving under the influence of psychoactive substances. It reported its research results at the end of 2011.

The prevention of driving under the influence of drugs is included as one of the key actions in the recent EU drugs action plan 2013–2016. As part of its aim to provide factual, objective, reliable and comparable information on the drug situation and responses to drug use in Europe, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is updating its 2008 Insights publication on drug use, impaired driving and traffic accidents with the findings from the DRUID project and published literature from 2007 to early 2013. Together with the EMCDDA's 2012 thematic paper *Driving under the influence of drugs, alcohol and medicines — findings from the DRUID project*, the present report provides a comprehensive European picture on illicit drugs and medicines in connection with driving. Both the policymaker and the general reader will find here a commentary on the large number of studies that have been published on the topic in recent years, allowing an objective appraisal of the known effects of psychoactive substances on the ability to drive and an assessment of the extent to which drivers impaired by such drugs are present on the roads.

Although this edition of the EMCDDA Insights series does not intend to be definitive, I am pleased to present what I hope will be seen as an important signpost towards more effective solutions to the problem of driving under the influence of drugs.

Wolfgang Götz
Director, EMCDDA

Executive summary

This literature review provides a comprehensive report on the relationship between drug use, impaired driving and traffic accidents. It describes methodological issues (Chapter 1), presents the results of prevalence surveys among drivers and provides an overview of findings from major international epidemiological surveys published since 2007 (Chapter 2) and gathers evidence from experimental and field studies of the relationship between drug use, driving impairment and traffic accidents (Chapter 3).

The research methods can be broadly separated into experimental and epidemiological studies. Every approach has its inherent advantages and disadvantages. Experimental studies, in which the drug is administered in measured doses to volunteers, may be conducted in a laboratory or a driving simulator or on the public road. They allow the effects of a single factor to be measured, but can identify only potential risks, and in some cases the results can be of limited value because of the use of non-realistic doses for safety reasons or because of the drug use history of the volunteers or inter-individual differences. Epidemiological studies examine the prevalence of drug use in various populations. They include roadside surveys, studies assessing the prevalence of drugs in a subset of drivers, accident risk studies, responsibility analyses, surveys among the general population and pharmacoepidemiological studies. However, the study design means that it is not possible to completely eliminate all risk factors other than that under examination and which may be highly correlated with the risk factor of interest. The results of different studies may not be comparable if, for example, different populations or different kinds of samples are tested.

The results of experimental studies have indicated that several illicit drugs could have an influence on driving performance; the effects of some, but not all, drugs are dose dependent. Cannabis can impair some cognitive and psychomotor skills that are necessary to drive. 3,4-Methylenedioxymethylamphetamine (MDMA) exerts both negative and positive effects on performance, and studies investigating the effects of a combination of alcohol and illicit drugs have found that some illicit drugs (e.g. cannabis) can act additively with alcohol to increase impairment, while others (e.g. cocaine) can partially reverse alcohol-induced impairment. MDMA can diminish some, but not all, deleterious effects of alcohol, while other negative effects of alcohol can be reinforced. The chronic use of all illicit drugs is associated with some cognitive and/or psychomotor impairment, and can lead to a decrease in driving performance even when the subject is no longer intoxicated. The results of experimental studies also show that some therapeutic drugs can cause obvious impairment. Benzodiazepines, for example, generally have impairing effects, but some types (whether long-, medium- or short-acting) cause severe impairment, whereas others are unlikely to have residual effects in the morning. First-generation antihistamines are generally more sedating than second-generation ones, though there are exceptions in both groups. Tricyclic antidepressants cause more impairment than the newer types, though the results of experimental tests after consumption of selective serotonin reuptake inhibitors are not always consistent. In every therapeutic class, however, some substances are associated with little or no impairment. These therapeutic drugs should preferably be prescribed to those wishing to drive.

Epidemiological studies have confirmed many of the findings from experimental studies. The Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) project has calculated that, on average, 3.48 % of drivers in the European Union drive with alcohol (> 0.1 g/l) in their blood, 1.9 % with illicit drugs, 1.4 % with (a limited list) of medicinal drugs, 0.37 % with a combination of alcohol and drugs and 0.39 % with different drug classes. Studies assessing the prevalence of drugs, medicines and/or alcohol in drivers who were involved in a traffic accident (fatal or otherwise) have found that alcohol is more prevalent than any other psychoactive substance, but drugs are also frequently found, and

in a higher proportion of drivers than in the general driving population. Of the drugs analysed, cannabis is the most prevalent after alcohol, although benzodiazepines, when samples have been analysed for these, are sometimes even more prevalent than cannabis. Statistically, the use of amphetamines, cannabis, benzodiazepines, heroin and cocaine is associated with an increased risk of being involved in and/or responsibility for an accident, and in many cases this risk increases when the drug is combined with another psychoactive substance, such as alcohol.

From the perspective of traffic safety — especially looking at prevalence rates and risks — the following conclusions can be made. Alcohol, especially in high concentrations, must remain the principal focus of prevention measures. The combination of alcohol and drugs or medicines seems to be a topic that should be addressed more intensively because it is associated with a very high risk of a traffic accident. The problems resulting from medicine use among drivers should be addressed by providing doctors and patients with appropriate information, not by defining thresholds. Based on experimental studies, Δ^9-tetrahydrocannabinol and amphetamines would appear to represent a minor risk, but in case–control studies amphetamines use is associated with a much increased risk of accident. More research is needed to investigate the probable risks of amphetamines in real traffic and the mediating factors. From the perspective of risk, sleep deprivation should also be addressed as it is associated with a high risk of accidents.

Introduction

In many EU Member States, the role of drugs in driver impairment and traffic accidents has been a cause for concern and an object of research for several decades. The Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) project calculated that, on average, 3.48 % of drivers in the European Union drive with alcohol in their blood, 1.9 % with illicit drugs, 1.4 % with (a limited list) of medicinal drugs, 0.37 % with a combination of alcohol and drugs and 0.39 % with a combination of different drug classes (EMCDDA, 2012). Large differences were observed among countries, with more alcohol and illicit drugs found in southern Europe and more medicinal drugs in northern Europe.

The first report by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 1999) on drugs and driving reviewed the available studies evaluating the relationship between drug use, impaired driving and traffic accidents for a large range of psychoactive substances. It also reviewed Member States' drug testing procedures and associated legislation on drug-impaired driving, as well as the issues raised by such testing. Among the report's conclusions was that more research — both experimental and epidemiological — was needed for a better understanding of the effects of drugs on the ability to drive. It was also suggested that psychomotor tests and roadside screening devices needed to be further developed in order to improve procedures for detecting impaired drivers.

The European action plan on drugs 2000–2004 reflected this need, calling for research into the effects of driving under the influence of illicit drugs and certain psychoactive substances. By 2007, a wealth of European and world research had addressed the issue and an update of the EMCDDA (1999) report was published. The main objectives of that report were to review the knowledge on driver impairment resulting from drug use from experimental and epidemiological studies published between 1999 and 2007, to underline the strengths and limitations of the different types of studies and to report on current levels of prevalence found in various subsets of drivers on EU roads. This literature review was published in 2008 as an EMCDDA Insights, *Drug use, impaired driving and traffic accidents*, (EMCDDA, 2008) and included studies from Europe, Australia, Canada and the United States. The report encompassed the main psychoactive substances found in Europe: cannabis, opioids, amphetamines, cocaine, benzodiazepines and other medicines (antihistamines, antidepressants) and other synthetic drugs.

At the start of the European Union's third Road Safety Action Programme 2003–2010, it was estimated that about 25 % of fatalities on European roads were the result of the influence of alcohol, but a lack of comparable studies meant that the proportion caused by the effects of illicit drugs or psychoactive medicines was unknown. Non-standardised studies of the situation preclude any meaningful evaluation of the effectiveness of the various responses and countermeasures. The DRUID project was established for this reason, with the aim of estimating the size of the problem using harmonised data collection protocols established following an international expert meeting.

The DRUID project reported its results in 2011, necessitating an update of the EMCDDA's 2008 Insights, *Drug use, impaired driving and traffic accidents*. The current report is an update of the 2008 Insights, based on the findings of the DRUID project and the published literature from 2007 to the end of January 2013. The new results have been integrated with those presented in the 2007 report, and this publication focuses more on meta-analyses and systematic reviews (Asbridge et al., 2012; Dassanayake et al., 2011; Elvik, 2013; Grotenhermen et al., 2007; Li et al., 2012; Rapoport et al., 2009; Verster et al., 2006, 2011).

Chapter 1 addresses methodological issues pertaining to experimental and epidemiological studies on drugs and driving. Chapter 2 reviews surveys carried out in different parts of the world (since 2007), according to the type of drivers surveyed, and provides an overview of the differences found depending on, for example, the studies' sample, screening and design. Chapter 3 discusses the effects and risks in terms of driving for each substance considered. When available, results on polydrug use and association with alcohol are reported.

Despite the current focus in EU Member States and by researchers on rapid roadside testing devices, their efficacy and effectiveness are not addressed here. Several countries have passed laws to allow such drug testing; however, the European Union's roadside testing assessment projects (Rosita, Rosita-2 and DRUID) considered no device reliable enough for roadside screening, although there has been some progress in recent years (Verstraete, 2012).

Although the focus of the present report is drugs and driving, it should be kept in mind that the data from European studies clearly demonstrate that the main psychoactive substance endangering lives on the roads today is alcohol (EMCDDA, 2007), a fact that has been confirmed by the DRUID project.

How studies were selected for this report

A search was made in PubMed with the following medical subject heading (MeSH) terms or combination of these terms: 'cannabis'; 'tetrahydrocannabinol'; 'amphetamines'; 'methamphetamines'; 'MDMA'; 'opiate alkaloids'; 'morphine'; 'codeine'; 'fentanyl'; 'heroin'; 'methadone'; 'benzodiazepines'; 'zopiclone'; 'zolpidem'; 'zaleplon'; 'buprenorphine'; 'cocaine', 'antidepressants'; 'antihistamines'; 'histamine antagonists'; 'histamine H1 antagonists, non-sedating'; 'histamine H1 antagonists'; 'antidepressive agents'; 'antidepressive agents, second-generation'; 'antidepressive agents, tricyclic'; 'antimanic agents'; 'citalopram'; 'monoamine oxidase inhibitors'; 'serotonin uptake inhibitors'; '4-butyrolactone'; '4-hydroxybutyric acid'; 'accident, traffic'; 'adverse effects'; 'automobile driving'; 'motor vehicles'.

Examples of searches used:

((((((‘Morphine’[Mesh] OR ‘Buprenorphine’[Mesh]) OR ‘Methadone’[Mesh]) OR ‘Heroin’[Mesh]) OR ‘Fentanyl’[Mesh]) OR ‘Codeine’[Mesh]) OR ‘Tramadol’[Mesh]) AND (‘Automobile Driving’[Mesh] OR ‘Accidents, Traffic’[Mesh] OR ‘Motor Vehicles’[Mesh]) AND (‘2007/01/01’[PDAT]: ‘2013/01/31’[PDAT])

(‘Histamine Antagonists’[Mesh] OR ‘Histamine H1 Antagonists, Non-Sedating’[Mesh] OR ‘Histamine H1 Antagonists’[Mesh]) AND (‘Automobile Driving’[Mesh] OR ‘Accidents, Traffic’[Mesh] OR ‘Motor Vehicles’[Mesh]) AND (‘2007/01/01’[PDAT]: ‘2013/01/31’[PDAT])

((‘zolpidem’ [Supplementary Concept] OR (‘Benzodiazepines’[Mesh]) OR ‘zopiclone’ [Supplementary Concept]) OR ‘zaleplon’ [Supplementary Concept]) AND (‘Automobile Driving’[Mesh] OR ‘Accidents, Traffic’[Mesh] OR ‘Motor Vehicles’[Mesh]) AND (‘2007/01/01’[PDAT]: ‘2013/01/31’[PDAT])

(('Antidepressive Agents'[Mesh] OR 'Antidepressive Agents, Second-Generation'[Mesh] OR 'Antidepressive Agents, Tricyclic'[Mesh] OR 'Antimanic Agents'[Mesh] OR 'Citalopram'[Mesh] OR 'Monoamine Oxidase Inhibitors'[Mesh]) OR 'Serotonin Uptake Inhibitors'[Mesh]) AND ('Automobile Driving'[Mesh] OR 'Accidents, Traffic'[Mesh] OR 'Motor Vehicles'[Mesh]) AND ('2007/01/01'[PDAT]: '2013/01/31'[PDAT])

(((('Methamphetamine'[Mesh]) OR 'Amphetamine'[Mesh]) OR 'N-Methyl-3,4-methylenedioxyamphetamine'[Mesh]) AND ('Automobile Driving'[Mesh] OR 'Accidents, Traffic'[Mesh] OR 'Motor Vehicles'[Mesh]) AND ('2007/01/01'[PDAT]: '2013/01/31'[PDAT])

('Cocaine'[Mesh]) AND ('Automobile Driving'[Mesh] OR 'Accidents, Traffic'[Mesh] OR 'Motor Vehicles'[Mesh]) AND ('2007/01/01'[PDAT]: '2013/01/31'[PDAT])

('4-Butyrolactone'[Mesh] OR '4-hydroxybutyric acid' [Supplementary Concept]) AND ('Automobile Driving'[Mesh] OR 'Accidents, Traffic'[Mesh] OR 'Motor Vehicles'[Mesh]) AND ('2007/01/01'[PDAT]: '2013/01/31'[PDAT])

Only the references published since the writing of the EMCDDA Insights on *Drug use, impaired driving and traffic incidents* (EMCDDA, 2008) and those relevant for the updating of the report were taken into consideration.

CHAPTER 1

Methodological issues in determining the relationship between drug consumption, impaired driving and traffic accidents

Several methods are used to study driving under the influence of drugs. These can be largely divided into two groups, namely experimental and epidemiological studies. The methodology used in the various types of experimental and epidemiological studies, possible problems associated with these different methodologies and recent proposals will be described in this chapter.

Experimental studies

In experimental studies, the drug under study is administered in different doses to volunteers and the effects on performance are measured and compared with those resulting from administration of a placebo or a positive control (e.g. alcohol). The performance of the volunteers can be evaluated using tests that assess various psychomotor and cognitive functions, tests in a driving simulator or 'real' driving tests.

Although experimental studies can provide invaluable information, the reader should be aware of their limitations:

- Often the potency of the drug administered is lower than that of the same drug used on the street. For example, in performance studies of cannabis, low-potency cannabis with a maximum Δ^9-tetrahydrocannabinol (THC) content of 4 % is traditionally used. Ramaekers et al. (2006a) showed that high-potency cannabis (13 % THC) diminishes additional cognitive functions and has a more pronounced effect on performance than the low-potency cannabis used in previous studies. The concentration of THC in cannabis can be higher than 20 or 30 years ago because of new cultivation techniques (EMCDDA, 2004). This underlines the importance of using realistic doses to estimate the effects of drugs in real life.
- The route of administration can influence the results. For example, Higgins et al. (1990) found that intranasally administered cocaine improved performance on the digit symbol substitution test (DSST), while Rush et al. (1999) found no such effects with orally administered cocaine.
- Results are dependent on the delay between drug consumption and performance of the task. Dextroamphetamine ([1]) administered 3–4 hours before a movement estimation task has no effect on performance of the task (Silber et al., 2006), while MDMA administered 4–5 hours before the task impairs performance (Lamers et al., 2003). Other possible causes of discrepancies in results in these studies could include differences in drug type, dose and task.
- The results of experimental studies assessing acute effects of drugs among recreational drug users may be influenced by the subjects' drug use history. For example, Rush et al. (1999) found that oral cocaine had no effect on performance on the DSST, while two previous studies found that performance was improved. However, the subjects in both previous studies reported substantially less cocaine use than the subjects used by Rush et al. (1999), who suggested that their subjects were perhaps tolerant to the performance-improving effects of cocaine.
- The sensitivity of experimental studies to detect drug effects on performance may be reduced by inter-individual differences in a between-subject paradigm. This can be countered by using a within-subject design, comparing each subject's postdrug performance with their pre-test baseline

([1]) Dextroamphetamine, also known as dexamphetamine, is the *d* form of amphetamine (the new terminology refers to the *S*-form). See http://www.emcdda.europa.eu/publications/drug-profiles/amphetamine

performance (Swerdlow et al., 2003). Mattay et al. (2000) showed that, in healthy subjects, the behavioural and neurophysiological effects of dextroamphetamine are not homogeneous because of genetic variation and differences in baseline cognitive capacity.

- Experimental studies can identify only potential risks. The risk demonstrated in the experiment may not necessarily occur in real road traffic. The risk seen in a study might be qualitatively so small that it does not result in a crash, or it might be so severe that the subjects feel so impaired that they do not drive (Berghaus et al., 2007).

- Some limitations are inherent to a specific type of experimental study: performance tests, driving simulator tests and 'real' driving tests. These are described below.

The advantage of experimental research is that it offers the chance to work on far more differentiated questions and less frequently occurring risk factors than epidemiological research. Another advantage is that, with an adequate design, experiments can focus on a single causative factor, which is not the case for epidemiological research (Berghaus et al., 2007).

Performance tests

Subjects' performance may be evaluated with tests performed in a laboratory setting. These laboratory tests are intended to measure specific skills and abilities that are involved in driving. Several publications have reviewed the available tests (Baselt, 2001; Ferrara et al., 1994; Irving and Jones, 1992). The tests that are most often used can be divided into five major groups: cognitive, psychomotor, impulsivity, physiological and subjective evaluations.

Cognitive tests

Cognition is the conscious process of knowing or being aware of thoughts or perceptions, including understanding and reasoning. Cognitive tests can assess a variety of cognitive functions:

- Attention: these tests can be subdivided into simple and divided attention tasks. In a simple attention task, the subject is asked to monitor one process and to respond appropriately to specific stimuli. In a divided attention task, the subject is asked to monitor two or more simultaneous processes and to respond appropriately to specific stimuli.

- Auditory, time and visual perception: these tests assess perception ability. An example of an auditory test is the auditory discrimination test: a series of pairs of auditory tones is presented to the subject, who must indicate whether the second tone is higher or lower than the first. Time perception can be estimated by asking the volunteers to estimate the duration of a certain time interval. An example of a visual test is the assessment of visual acuity: the subject is shown a series of test patterns of increasing complexity or decreasing size and is asked to identify or discriminate between the patterns while distance, lighting conditions or degree of contrast may be varied.

- Information processing: these tests assess the ability of the volunteers to solve problems or to make decisions.

- Logical reasoning: a series of simple sentences, such as 'Birds grow on trees', is presented and the subject must indicate whether each statement is true or false.

- Memory: subjects' memory functioning (long- or short-term), such as delayed recall, episodic memory or working memory, is assessed.

- Vigilance: this task generally uses an electronic device that presents a visual stimulus moving in a rather monotonous pattern on a screen. The subject must observe and report deviations in this pattern over a prolonged period of time without feedback from the apparatus. An auditory pattern of signals may be used instead of a visual stimulus.

Cognitive tests specifically used in assessing the effects of a psychoactive substance on the ability to drive include:

- Benton visual retention test (BVRT): this assesses visual perception, visual memory and visual constructive abilities.

- Critical flicker fusion (CFF): the subject is asked to view one or more lights on a computer screen or electronic apparatus and to indicate whether the light appears to be flickering or is continuous. The rate of flicker is constantly increased or decreased, and the frequency of the subject's discriminative threshold is recorded.

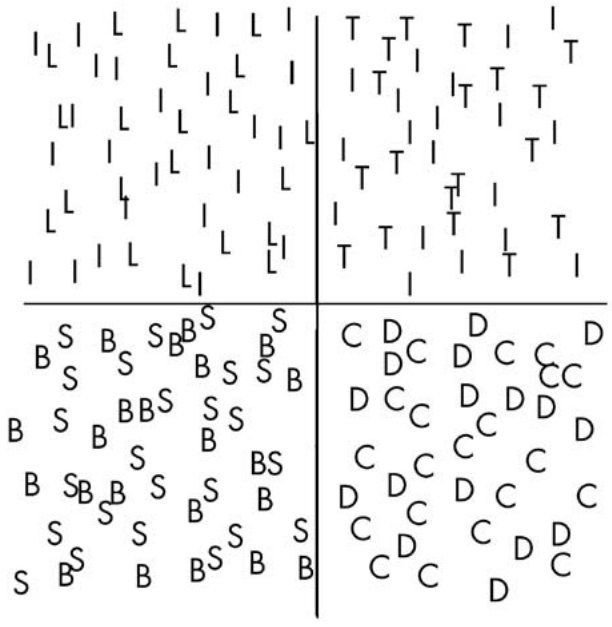
- Digit symbol substitution test (DSST): the subject is shown a code sheet containing a series of numbers assigned to a series of symbols. Afterwards, the subject is shown the symbols in random order and is asked to assign the corresponding number. During repetitions of the task, the pattern of the digit–symbol pairings is usually scrambled.

- Hopkins verbal learning test: the subject repeats as many words as he or she can recall from a list of words that was read by the instructor. Afterwards, the instructor reads another list of words and the subject has to respond with 'yes' if the word was on the first list and 'no' if it was not.

- Learning memory task (LMT): a list of 21 simple, concrete and familiar words must be learned in four attempts. The words are presented on a computer screen in lower-case letters at a rate of one word every 500 milliseconds, without any gaps between stimuli. The words are presented in a different order at each attempt. At the end of each presentation, the subject makes an immediate free recall. The subject is asked for a delayed free recall of the words for 1.5 minutes, about 1 hour after learning.

- Letter cancellation test: the subject is given a page filled with random letters and is asked to strike through one or more specific target letters whenever they appear (Figure 1).

FIGURE 1
Four examples of a letter cancellation task



- Mini-mental state examination (MMSE): this is a tool for measuring global cognitive function. It is an 11-question measure that tests orientation, registration, attention, calculation, recall and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment. The MMSE takes only 5–10 minutes to administer and is therefore practical to use repeatedly and routinely.

- Paced auditory serial addition task (PASAT): this measures working memory. It requires addition of simple digits presented verbally in a series with a successively higher pace of presentation. The task reflects the capacity for divided attention, is a measure of information processing speed and appears to be sensitive to minor attention deficits.

- Rapid visual information processing task (RVIPT): this is a test of sustained attention, during which single digits are presented in quick succession (100 or 200 digits per minute) on a computer screen. When target sequences of numbers are be identified, the subject presses a button.

- Repeated acquisition task: the subject is given the opportunity in a series of trials to learn the appropriate responses to a collection of images. Following a specific interval, the subject is then tested on his or her ability to recall the previously acquired responses.

- Sternberg test: this test explores short-term memory and working memory. A series of two to six numbers is presented to the subject, followed immediately by a target number. The subject indicates as rapidly as possible whether the target number was part of the list to be memorised.

- Stroop word/colour test: the subject is asked to depress one of four keys labelled with a different colour in response to a stimulus. The stimulus is the name of one of the four colours or of a non-represented colour or does not represent a colour at all.

- Time wall test: during this test of time estimation, subjects observe a brick descending from the top of the computer screen at a constant rate towards a target at the bottom of the screen. The target disappears behind a brick wall about two-thirds of the way down the screen. The subject responds by pressing a designated key at the exact time that he or she estimates the object contacts the target.

- Tower of London task: this measures planning function. The subject is asked to plan mentally a sequence of moves to match a start set of discs to a goal, and then to execute the moves one by one (Figure 2).

- Wechsler adult intelligence scale (WAIS): this is a comprehensive test of cognitive ability for adults — a general test of intelligence. It is made up of 14 subtests, comprising verbal (seven subtests: information, comprehension, arithmetic, similarities, vocabulary, digit span, letter–number sequencing) and performance scales (seven subtests: picture completion, digit symbol-coding, block design, matrix reasoning, picture arrangement, symbol search, object assembly).

- Wisconsin card sorting test (WCST): this measures abstract conceptual skills, cognitive flexibility and ability to test hypotheses, and utilises error feedback. The subject sorts 128 cards that depict coloured, numbered shapes into four categories using accuracy feedback given after each trial. The criterion for correct categorisation changes whenever 10 consecutive cards are sorted correctly.

Psychomotor tests

Psychomotor tests assess movements that are generated by stimulation of certain parts of the brain.

- Body sway: measurements of body movement of the subject with or without his or her eyes closed are usually taken in both the lateral and sagittal directions over a specified period of time using some type of metering device, such as an electronic platform.

- Motor coordination: the finger-tapping test (FTT) assesses motor speed and motor control. Other tests assess the motor response of volunteers to a certain visual or auditory stimulus:

  – The circular lights task (CLT) typically employs an electronic device with a series of 10–20 lights arranged in a circular pattern. The lights are illuminated in random order, and the subject must trigger a switch corresponding to that light.

  – The grooved pegboard test is a manual dexterity test consisting of a board containing holes with randomly positioned slots. Pegs with a key along one side must be rotated to match the hole before they can be inserted.

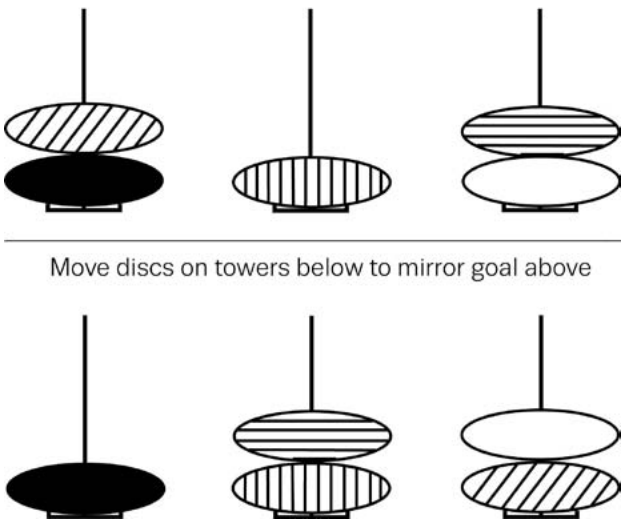
  – During the trail-making test (TMT), the subject is shown a page containing jumbled numbers or letters, and is asked to connect the numbers in numerical sequence or the letters in alphabetical sequence. Accuracy and time to complete the task are assessed.

  – During the simplest form of a tracking task, the subject is asked to control the position of a light bar on a screen using a hand-operated device. More sophisticated versions involve variable speed control of the visual stimulus and/or a computerised representation of a vehicle moving along a road. For example, during the critical tracking test (CTT), the subject is asked to control the position of a light bar on a display screen using a steering wheel or joystick. The instability of the bar gradually increases until the subject reaches a threshold of ability to control its position. In the compensatory tracking test, subjects are also required to track a moving arrow on a visual display unit, but in addition a peripheral awareness task is included in which the subject responds to a stimulus presented in the periphery of vision while simultaneously attending to the tracking test.

- Reaction time: Several tests exist to measure psychomotor speed:

  – The simple reaction time (SRT) is the interval elapsing between the brain receiving a sensory impression (visual, auditory or somatosensory) and the execution of a movement in response to that impression.

FIGURE 2
A Tower of London test



- In a choice reaction time (CRT) task, a series of stimuli, which may be auditory and/or visual, is presented to the subject using an electronic apparatus or a computer screen. The subject is instructed to respond appropriately and rapidly through hand or foot movements to preselected signals. The test may include disturbance signals to distract the subject, and it may involve two or more simultaneous tasks. The subject is graded on speed and accuracy. Three components of reaction time are measured: the motor reaction time (MRT) between the start and response buttons, the total reaction time (TRT) from stimulus onset to completion of response and the processing or recognition reaction time (RRT), obtained by subtracting the MRT from the TRT.

- A go/no go task can be used to assess reaction time instead of impulsivity (see below).

- The serial reaction time task produces sequence learning through repetition of uncued and unannounced serially ordered stimuli. Learning is assessed by observing a deterioration in task performance when a random sequence replaces a regularly repeating sequence.

Impulsivity tests

Some performance tasks are behavioural measures of impulsivity:

- In a go/no go task or a stop signal task, the subject is asked to respond to one particular event (e.g. a red colour or a horn sound) but ignore other events (e.g. a blue colour or a rooster sound).

- The Iowa gambling task measures decision-making and risk sensitivity as defined by the inability to anticipate and reflect on the consequences of decision-making. The subject sees four decks of cards on a computer screen labelled A, B, C and D. The gains and losses for each card selection are set so that in each block of 10 cards from deck A or B over the course of the trials there is a total gain of USD 1 000, interspersed with unpredictable losses totalling USD 1 250. For decks C and D, the gains and losses for each card selection are set so that in each block of 10 cards there is a total gain of USD 500, interrupted by losses totalling USD 250. Thus, decks A and B are 'disadvantageous' in the long term whereas decks C and D are 'advantageous'. One dependent measure is collected from this task: net score (the total number of cards picked from C and D minus the total number of cards picked from A and B).

Physiological measurements

The parameters that can be assessed include eye movements, pupillary response (miosis, mydriasis), pulse, blood pressure and tunnel vision. Electroencephalography (EEG) can also be used. The Maddox wing device is sometimes used to measure the balance of the extraocular muscles; it quantifies exophoria as an indicator of extraocular muscle relaxation and esophoria as an indicator of extraocular muscle tension.

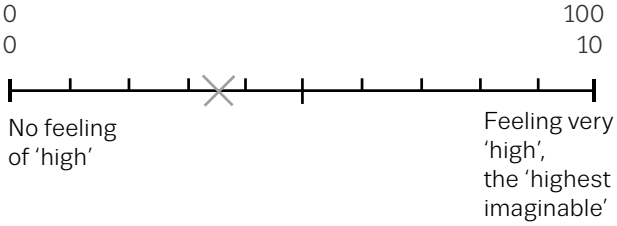
Subjective evaluations

In some experimental studies the subjects report their own observations on visual analogue scales. These scales measure a characteristic or attitude that is believed to range across a continuum of values. Visual analogue scales can be indicative of both pleasant (e.g. drug liking, increased calmness) and unpleasant (e.g. 'feel bad', 'nauseous', sedation, pain) effects of a drug. The line analogue rating scale (LARS) consists of 10-cm line analogue scales on which the subjects indicate their present feeling (concerning sedation) relative to a mid-point that represents their normal state of mind before treatment was started (Figure 3). Another example is the Stanford sleepiness scale, a seven-level measurement in which subjects select a specific statement best describing their state of sleepiness.

There are limitations inherent to studies that use performance tests. First, these tests measure only a part of the performance needed to complete a task and do not cover driving ability as a whole. Second, the selection of specific tests can influence the results of the study. For example, when the effect of the combination of cannabis and alcohol is studied, some studies find an additive or even synergistic effect, while other studies find the opposite. Liguori et al. (2002)

FIGURE 3

A visual analogue scale for the subjective feeling of 'high'



found no significant additive effects of alcohol and cannabis on brake latency. According to the authors, this might have been because of the use of reaction time as the key dependent variable, as several other studies found additive or multiplicative cannabis and alcohol effects on other aspects of performance, such as visual search and road tracking (Lamers and Ramaekers, 2001; Sexton et al., 2002). Ramaekers et al. (2006a) found that THC use did not affect performance on the Iowa gambling task; however, the sensitivity of this task to acute drug effects may be low as the task was never specifically designed for this purpose.

Driving simulator and 'real' driving tests

Driving performance can be evaluated using tests in a driving simulator or 'real' driving tests. In a driving simulator, subjects perform a computer simulation of a driving task. Hoffman and Buld (2006) described and evaluated the design of a driving simulator. The main advantages of driving simulation are that driving tasks can be standardised and data can be obtained safely. However, because a real environment can never be fully replicated in a simulator, subjects must compensate for the incomplete driving environment, delays and distortions in the graphics and for having to act in two different worlds. Since this often cannot be achieved immediately, subjects need a dry run to learn how the simulator works. A major problem during dry runs is so-called 'simulator sickness': nausea that can be mild to severe and lasts a few minutes to several hours, possibly resulting in inadequate driving behaviour, whether consciously or not. As a consequence, both the internal and the external validity are limited and the acceptance of the method itself is likely to decrease. Experience shows that repeated exposure to the simulator situation usually reduces physical discomfort; however, empirical studies are very rare. Equally detailed information concerning dry runs is not consistently given in studies using driving simulation, and, if so, the dry runs may vary in length from 5 minutes to several hours. Commonly used guidelines do not exist. Hoffmann and Buld (2006) assessed the effectiveness of a training programme, consisting of a familiarisation phase followed by special exercises (braking, accelerating, steering, driving on a motorway, turning at intersections and a final driving test), in reducing dropout rate. They found that without the simulator training programme the dropout rate as a result of nausea was quite high, whereas no subject who received training dropped out. The authors concluded that extensive training is necessary to be able to drive satisfactorily in a simulator. Several situations can be simulated, including (Sexton et al., 2002):

- Pulling-out events: these are situations where a car pulls out in front of the driver's car. The driver takes avoiding action that can be detected and a reaction time is estimated.
- Braking events: these events are controlled in a similar way to pulling-out events, except that the trigger vehicle brakes at a certain distance from the driver's car.

The test that best assesses the effects of using a psychoactive substance on driving performance is a 'real' driving test. The test can be performed in the presence or absence of normal traffic, but one disadvantage is the necessity of taking traffic safety into consideration. A 'real' driving test can be more sensitive than laboratory tests in assessing impairment of driving ability. For example, Veldhuijzen et al. (2006a) evaluated the effect of chronic non-malignant pain on driving performance. An on-the-road driving test showed significant differences in driving performance between drivers with chronic pain and drivers with no chronic pain, whereas laboratory tests did not.

The outcome measures used to assess performance during a driving simulation test or a 'real' driving test include (de Waard et al., 2000; Ramaekers et al., 2004; Sexton et al., 2000; Veldhuijzen et al., 2006a):

- Standard deviation of the lateral position (SDLP): this parameter measures the extent to which the car 'weaves' within a traffic lane. It is reasonable to assume that SDLP represents overall highway driving ability since it encompasses several levels of information processing which are combined in an integrated driving model. For example, whereas basic vehicle control, such as road tracking, involves automatic or effortless performance, negotiation of common driving situations, such as curves, intersections and gap acceptance, requires controlled processing and thus more effort. In addition, the test measures motivational aspects, such as the risks subjects are willing to take, and subjects' ability to evaluate risk. As SDLP increments ultimately result in lane crossing into the adjacent traffic lane, it can be regarded as an index of driving safety. Sexton et al. (2000) showed that SDLP in the road-tracking test was the most sensitive measure of the adverse effects of THC on driving ability.
- Standard deviation of speed.
- Mean speed.
- Mean lateral position.

- Car following: in a 'real' driving test, the subject may be asked to follow a car driven by the investigator.
- Brake reaction time (BRT).
- Gap acceptance: this parameter measures whether or not judgement is impaired.
- Accident involvement.

Epidemiological studies

Epidemiological studies on drugs and driving examine the prevalence of drug use in various driving populations. Some studies investigate the prevalence of drug use in the general driving population, while others focus on certain subpopulations, such as persons admitted to a hospital emergency department. By comparing the prevalence of a certain drug among the general driving population with the prevalence among persons admitted to an emergency department, an estimation can be made of the risk of injury as the result of a traffic accident while under the influence of a certain drug: these figures indicate whether a person under the influence of the drug has a higher risk than a sober person of being injured in a traffic accident. Responsibility studies calculate the risk of being responsible for a traffic accident while driving under the influence of a drug.

The prevalence of drugs in various populations can be assessed by analysing biological samples of the involved subjects, or by conducting surveys or pharmacoepidemiological studies.

Epidemiological research is, however, limited because there may be risk factors associated with drug use that do not emerge from the study findings. This may be because the appropriate study design (e.g. a long-term study or a multicentre study) is difficult to put into place from a methodological point of view (because of a change in screening methods, lack of homogeneity of data, etc.). Another disadvantage of epidemiological research is that it is not able to distinguish between a 'real' risk factor and other factors that may be highly correlated with the risk factor (Berghaus et al., 2007).

Epidemiological studies are also difficult to compare with each other because of several kinds of differences among them, such as the following:

- The sample populations are different. They can differ in several sociodemographic factors, such as age and gender. One study which reported results of drivers who were killed in traffic accidents in France included only drivers under the age of 30 years and found a much higher proportion of cannabis-positive samples than other similar studies (Mura et al., 2006).
- The time at which the studies are performed can differ. Not only can the year in which samples are collected differ, but so can the day of the week. Studies conducted on weekend nights find higher percentages of drug-positive drivers than studies conducted over the whole week (Mathijssen, 1999).
- Biological samples are analysed for different types of psychoactive substances. For example, for benzodiazepines, opioids and amphetamines, prevalence results can depend upon the number and types of substances that are searched for in the samples. In Norway, a study assessing benzodiazepines in drivers suspected of driving under the influence of drugs reported only the percentage of samples that were positive for diazepam and flunitrazepam (Christophersen, 2000), while in a study in Switzerland the samples were analysed for diazepam, desmethyldiazepam, midazolam, oxazepam and lorazepam (Augsburger et al., 2005). For cannabis detection, some studies test only for the presence of THC, while others test for the THC metabolites THC-COOH (11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid) or 11-OH-THC (11-hydroxy-Δ^9-tetrahydrocannabinol) or for several metabolites. As the detection time of these metabolites differs, the choice of the substances tested for can influence the results of the study (Verstraete, 2004).
- Different types of biological samples are used, with varying detection times. The use of urine samples can pose some problems. As the metabolites of cannabis can be detected in urine for a relatively long period of time following consumption, their presence in urine does not necessarily mean that the subject was under the influence of the drug at the time of sampling; this can lead to different results from when blood or saliva is sampled (Verstraete, 2004). It is important to have 'equivalent' cut-offs for different types of samples to ensure that measurements of drug prevalence based on samples of blood and oral fluid taken simultaneously are comparable (Gjerde and Verstraete, 2010, 2011).
- Different analytical techniques are used to analyse the samples, with different limits of detection and quantification.

- Different cut-off levels are used. For alcohol detection, for example, the cut-off level used to define a positive sample can range from 0.1 g/l (Logan, 2005; Logan and Schwilke, 2004; Plaut and Staub, 2000) to 0.8 g/l (Assum et al., 2005; Brault et al., 2004; del Rio et al., 2002; Longo et al., 2000a).

In what follows, the methodology and limitations of the various types of epidemiological studies are described.

Roadside surveys

Roadside surveys investigate the prevalence of psychoactive substances among the general driving population. Drivers are randomly stopped and tested for the presence of alcohol, drugs and/or certain medicines in their body.

The results of these studies become more representative for the general driving population as the number of included drivers increases. Some studies try to make the results more representative by weighting them according to traffic flow (Assum et al., 2005). The study design can greatly influence the results. In addition, roadside surveys are expensive to conduct, as a large number of drivers need to be screened. Moreover, this type of epidemiological study cannot be conducted in every country as there may be legal obstacles to screening drivers without suspicion.

Subsets of drivers

Epidemiological studies may also look at only a subset of drivers, rather than the general driving population:

- Injured drivers: biological samples are collected from drivers admitted to hospital over a given period of time, and analysed in order to assess the involvement of drugs, medicines and/or alcohol in accidents. These studies should take into consideration the possibility that certain medications, particularly benzodiazepines and opioids, may have been administered at the crash site or in hospital before the samples were taken.

- Drivers killed in accidents: for these epidemiological studies, the involvement of drugs, medicines and/or alcohol in fatal accidents is assessed using samples from drivers who were killed in a traffic accident. Here, too, there is a need to determine whether positive test results for medicines were because of initial use by the driver or a result of therapeutic administration during emergency care or resuscitation efforts.

- Drivers involved in a traffic accident: samples are collected from all drivers who were involved in a traffic accident. In some studies, only fatal accidents are included.

- Drivers suspected of driving under the influence of drugs: the methodology of these studies can vary in several ways, as the testing procedure varies by country. For example, in some countries a field sobriety test is used, while in others it is not. This field sobriety test can consist of different tests, and various on-site drug screening tests can be used.

- Drivers suspected of driving under the influence of alcohol: in these 're-analysis' studies, samples that were initially collected for alcohol detection are later tested for the presence of drugs, medicines and alcohol.

Thus, studies that try to assess the prevalence of psychoactive substances in drivers who were injured or killed in a traffic accident must be able to determine whether positive test results for medicines are due to pre-injury use or administration of medicines after admission.

Surveys

Surveys about driving under the influence of drugs, medicines and/or alcohol are conducted over the telephone or in face-to-face interviews. Examples of questions asked are 'Have you ever driven a vehicle under the influence of alcohol or drugs?', 'Have you ever driven a vehicle shortly after the use of alcohol or drugs?', 'Have you ever been involved in an accident while under the influence of alcohol or drugs?', etc. Some surveys include the general driving population, while others focus on a subpopulation such as young drivers or drug users. Information gathered in surveys should, however, be interpreted in the light of several limitations. Subjects may, for example, be unwilling to divulge certain information, misunderstand the questions or forget events (McGwin et al., 2000).

Accident risk analyses

The accident risk associated with the use of drugs, medicines and/or alcohol can be assessed by comparing their prevalence among the general driving population

(controls) with the prevalence among drivers who were injured, killed or involved in a traffic accident (cases).

The accident risk can be expressed in various ways, such as an odds ratio (OR) or relative risk (RR). ORs and RRs are calculated as follows, assuming that the data are available as in Table 1:

$$RR = \frac{a}{a+b} \times \frac{c+d}{c}$$

$$OR = \frac{a}{c} \times \frac{d}{b}$$

Mostly, data for the control group ($b + d$) are collected using roadside surveys. Some studies use a different methodology, for example using samples from drivers who were hospitalised for reasons other than a traffic accident as control samples (Mura et al., 2003). Other studies may use questionnaire survey results rather than biological sample analysis to calculate accident risks (Asbridge et al., 2005; Blows et al., 2005; Fergusson and Horwood, 2001; Gerberich et al., 2003; Jones et al., 2005; Wadsworth et al., 2006).

One limitation of using questionnaire data to calculate accident risk is a possible underestimation of the prevalence, while with biological sample collection there may be a high percentage of refusals. As most of the substances under investigation are illicit, potential control subjects who are users are more likely than non-users to refuse to supply a sample. This would result in bias of the results by showing a stronger positive association between the drug and crash risk than is really the case. As, generally, the proportion of non-crash drivers who test positive for drugs is likely to be small, even a relatively small proportion of potential control subjects who do not supply a sample would throw study results into serious doubt (Bates and Blakely, 1999). Van der Linden et al. (2012) found that subjects who gave an oral fluid sample but refused to give a blood sample were three times more likely to test positive for drugs.

TABLE 1

Symbolic presentation of the data used to calculate accident risks

Drugs	Accident		
	Yes	No	Total
Yes	a	b	$a + b$
No	c	d	$c + d$
Total	$a + c$	$b + d$	n

Ramaekers (2003a) discusses two possible pitfalls in estimating drug-related crash risk. First, a case–control analysis does not necessarily take into account the effects of dose or treatment duration when estimating the crash risk following medicine use. The possibility therefore exists that the failure to find a positive association between, for example, the use of tricyclic antidepressants (TCAs) and accidents may merely reflect the occurrence of tolerance in drivers after prolonged treatment, while a positive association might have been found in drivers who were just starting antidepressant treatment. Second, the study's statistical power may be insufficient to detect significant proportional differences, as the prevalence rates of drugs in the samples under study are mostly low and sample sizes are limited.

Lenguerrand et al. (2008) studied the disparities between the quasi-induced exposure (QIE) method and a standard case–control approach with crash responsibility as variable of interest, based on the Stupéfiants et Accidents Mortels [Illicit Drugs and Fatal Crashes] (SAM) study. The QIE method selects only 'clean crashes', i.e. two-vehicle crashes in which one driver is declared entirely responsible and the other entirely not responsible. Drivers who are identified as 'not responsible' are assumed to be passively crash involved and to have been randomly 'selected' by 'responsible' drivers from among the driver population. The prevalence of a given risk factor among not-responsible drivers is assumed to be a good proxy for its prevalence among the whole driver population present at the times and locations of crashes ([2]). While both approaches found that being under the influence of alcohol or cannabis increased the risk of drivers causing a fatal crash, the two approaches were not equivalent. They differ mainly with regards to the driver sample selected. The QIE method results in the overall road safety issue being split into two substudies: a matched case–control study dealing with two-vehicle crashes and a case–control study dealing with single-vehicle crashes but with a specific control group. The standard case–control approach studies drivers involved in all type of crashes whatever the distribution of the responsibility in each crash. This method, also known as 'responsibility analysis' (see the following subsection), is the most relevant for assessing the overall road safety implications of a driver characteristic.

([2]) The SAM study is a population-based case–control study that analysed more than 17 000 accidents and almost 11 000 drivers involved in fatal accidents between September 2001 and September 2003 in France. It was based on a quasi-exhaustive sample of road accidents (all the instantly fatal accidents that took place during the 2 years studied) and included drivers who were killed, injured or unhurt.

Houwing et al. (2013) studied the origin of the variation between the ORs calculated in the different countries in the Driving under the Influence of Drugs, Alcohol and Medicine (DRUID) project. Differences between the ORs in the DRUID case–control studies were (partially) explained by random and systematic errors. Selection bias and errors as a result of small sample sizes and small numbers in some categories were the most frequently observed errors in the six DRUID case–control studies. Therefore, Houwing et al. recommended that epidemiological studies that assess the risk of psychoactive substances in traffic pay specific attention to avoid these potential sources of random and systematic errors.

Responsibility analyses

Responsibility analyses investigate whether there is an association between driving under the influence of drugs, medicines and/or alcohol and responsibility for a traffic accident. The prevalence of these substances among drivers who were responsible for a traffic accident (cases) is compared with the prevalence among drivers who were involved in, but not responsible for, a traffic accident (controls).

There are a number of limitations to responsibility analyses:

- In some cases, the true source of the responsibility can be misjudged, and this might cause a misclassification bias, which may lead to an underestimation of the real relative risk (Dussault et al., 2002).
- The control group consists mostly of crash-involved but 'not responsible' drivers. Some of the drivers who were judged 'not responsible' may, in fact, have borne some responsibility, as they failed to avoid the crash. The ideal control group would consist of drivers who were not involved in crashes but who were on the road under similar circumstances of time and place (Lowenstein and Koziol-McLain, 2001).
- A major limitation when fatally injured drivers are included is the high percentage of responsible drivers among the drug-free group. This high baseline figure means that it is difficult to find statistically significant differences between drug-free and drug-positive drivers with respect to their level of responsibility. One of the benefits of using non-fatally injured drivers is that the percentage of drug-free drivers judged responsible for the crash is generally much lower (Longo et al., 2000b). For example, in two studies of non-fatally injured drivers, the percentage of drug-free drivers judged responsible for the crash was 53 % (Longo et al., 2000b) and 48 % (Lowenstein and Koziol-McLain, 2001), while it was 71 % in a study of fatally injured drivers (Drummer et al., 2004).

Pharmacoepidemiological studies

Pharmacoepidemiological studies compare the involvement in traffic accidents of drivers using a certain medication with that of a control group not using the medication, in order to assess the driving risks associated with medication use. Most of these types of studies gather information through databases, such as prescription records, police reports, health insurance records and databases from hospitals, but some studies gather information in another way, by interviewing people, for example. McGwin et al. (2000) used the following methodology to evaluate the association between elderly drivers' medication use and their risk of responsibility for an accident. A total of 901 drivers aged 65 years and older were selected from the Alabama Department of Public Safety driving records, including 244 at-fault drivers involved in crashes, 182 not-at-fault drivers involved in crashes and 475 drivers not involved in crashes. Information on demographic factors, chronic medical conditions, medications used, driving habits, visual function and cognitive status was collected by telephone interview. Frequency distributions were calculated for subjects involved in and those not involved in crashes, and crude ORs and 95 % confidence intervals (CIs) were computed for the use of different types of medicines. The results showed the various accident risks associated with the use of different medications.

Several possible limitations are inherent to pharmacoepidemiological studies:

- The use of databases as a source of information can be a limitation. For example, not all traffic accidents are reported to the police, which can lead to an underestimation of accident rates in the studied population when using police reports (Barbone et al., 1998). In addition, databases do not contain all possible information on other risk factors, such as alcohol use (Neutel, 1998).
- Bias might result from the subjects' patterns of medication use, such as non-compliance, or irregular as opposed to continuous use (Hemmelgarn et al., 1997).

- Some studies do not control for unmeasured variation within an individual, and thus cannot differentiate between the risks associated with use of the medication and those associated with the underlying disorder being treated by the medication (Barbone et al., 1998).

- Driving patterns might differ between periods of use and non-use of a medication, such as choosing not to drive while using the medication. This could lead to an underestimation of the risks of driving associated with use of the medicine (Barbone et al., 1998; Hemmelgarn et al., 1997).

- Gathering information by interview or questionnaire is limited by the restrictions that are inherent to such surveys (see previous subsection on surveys).

The DRUID project developed a model for integration of results of epidemiological and experimental studies based on a reference curve for alcohol: alcohol data obtained with different study methodologies are used as the gold standard (Hargutt et al., 2011).

Meta-analyses

Meta-analysis is a statistical technique used to combine the findings from independent studies. Meta-analyses are most often used to assess the clinical effectiveness of healthcare interventions by combining data from two or more randomised controlled trials. The validity of the meta-analysis depends on the quality of the systematic review on which it is based. Good meta-analyses aim for complete coverage of all relevant studies, look for the presence of heterogeneity and explore the robustness of the main findings using sensitivity analysis. Systematic review methodology is at the heart of meta-analysis. This stresses the need to take great care to find all the relevant studies (published and unpublished) and to assess the methodological quality of the design and execution of each study. The objective of systematic reviews is to present a balanced and impartial summary of the existing research, enabling decisions on effectiveness to be based on all relevant studies of adequate quality. Data from a meta-analysis are usually displayed pictorially, a representation often referred to as a forest plot, which displays the findings from each individual study as a dot or square, with squares towards the left side indicating the new treatment to be better, whereas those on the right indicate the new treatment to be less effective. The size of the dot or square is proportional to the precision of the study (roughly speaking, the sample size). A horizontal line (usually the 95 % confidence interval) is drawn around each of the studies' squares to represent the uncertainty of the estimate of the treatment effect. The aggregate effect size, obtained by combining all the studies, is usually displayed as a diamond.

Assessments of the quality of systematic reviews and meta-analyses often identify limitations in the ways in which they were conducted. Flaws in meta-analyses can arise through failure to conduct any of the steps in data collection, analysis and presentation described above. To summarise the qualities of a robust meta-analysis:

- The search strategy should be comprehensive and likely to avoid bias in the studies identified for inclusion.

- The publication should be bias assessed.

- The quality of the individual studies should be assessed against an appropriate checklist of criteria.

- The combined effect size should be calculated using appropriate statistical methods.

- Heterogeneity should be considered and tested for.

Meta-analyses offer a systematic and quantitative approach to synthesising evidence to answer important questions. Nonetheless, pitfalls abound in the execution of meta-analyses and they are fundamentally limited by the quality of the underlying studies (Crombie and Davies, 2009).

Conclusion

There are broadly two different methods to study driving under the influence of drugs, namely experimental and epidemiological studies.

In experimental studies, subjects' performance is evaluated by laboratory performance tests, tests in a driving simulator or 'real' driving tests. Although these studies allow the assessment of the effects of a drug on differentiated functions, they can identify only potential risks, but with an appropriate design they can attribute the findings to a single cause. The results of these studies may be limited by the use of non-realistic drug doses or by inter-individual differences.

Performance tests are conducted in a laboratory setting and are intended to measure specific skills and abilities that are involved in driving, such as attention, vigilance, auditory and visual skills, reaction time, cognitive tests

and visual–motor coordination skills. They measure a part of the performance needed to complete a task, but do not cover driving ability as a whole. In addition, the selection of the test(s) to be performed can influence the results of the study, because the measure of the acute drug effect is related to the sensitivity of the test chosen.

In a driving simulator, subjects perform a computer simulation of a driving task. The main advantages of this type of study are that driving tasks can be standardised and data can be gained safely. However, because a 'real' environment can never be fully replicated, subjects must deal with certain difficulties in the driving simulation.

'Real' driving tests are able to most realistically show the effects of psychoactive drugs on driving performance. They can be conducted in the presence or absence of normal traffic. One main disadvantage of this kind of experimental study is the need to take into consideration the safety of other road users.

Because of small sample sizes and a multitude of variable factors in experimental studies, it is difficult to compare or combine the results of different studies.

Epidemiological studies on drugs and driving examine the prevalence of drugs in various driving populations. These studies include roadside surveys, prevalence studies in subsets of drivers, accident risk studies, responsibility analyses, surveys by interview and pharmacoepidemiological studies. Legislation, data protection, data availability and funding may affect the choice of type of survey. A roadside survey offers the closest representation of the general driving population.

In epidemiological research, the appropriate study design may be difficult to put into place because of limitations to the methodology, and there may be risk factors associated with drug use that do not emerge from the study findings. Moreover, epidemiological studies are not always easy to compare, if, for example, the data are from different populations, investigators use different types of samples or detection techniques or samples are tested for different psychoactive substances.

2

CHAPTER 2
Prevalence of drugs among drivers

In order to estimate the size of the danger that driving under the influence of drugs poses to traffic safety, it is necessary to assess the prevalence of driving under the influence of drugs. The epidemiological studies on drugs and driving published since 2007 are discussed in this chapter. A more detailed description of the types, methodology and limitations of these studies is given in Chapter 1.

Roadside surveys

Roadside surveys investigate the prevalence of psychoactive substances among the general driving population. Drivers are randomly stopped and tested for the presence of alcohol, drugs and/or medicines in their body.

The results of recent roadside surveys are given in Tables A1 and A2 (Appendix). Table A1 presents the results of the roadside survey performed during the DRUID project. Table A2 presents the results of other studies, most of which were performed outside Europe.

In the DRUID project, a roadside survey was conducted in 2009 and 2010 (see also EMCDDA, 2012). Oral fluid and blood were taken from nearly 50 000 drivers in 13 countries. Based on these results, a weighted average of the prevalence of alcohol and illicit and some medicinal drugs was calculated. The results for the different drug classes are summarised in Table 2. Overall, 7.43 % of European drivers had alcohol or one of the 23 tested drugs in their oral fluid or blood. Alcohol levels above 0.1 g/l and above 0.5 g/l were found in 3.5 % and 1.5 % of drivers, respectively.

TABLE 2

Weighted European mean of the prevalence of different substances in the general driving population

Substance	Weighted European mean (%)
Alcohol > 0.1 g/l ([1])	3.5
Alcohol > 0.5 g/l	1.5
Illicit drugs	1.9
Amphetamines	0.08
Cannabis	1.32
Cocaine	0.42
Opioids	0.07
Medicinal drugs	1.4
Benzodiazepines	0.90
Zopiclone and zolpidem	0.12
Medicinal opioids	0.35
Alcohol and drugs	0.37
Different drug classes	0.39

([1]) No alcohol results were available for Sweden. Alcohol-positive drivers (> 0.2 g/l) were dealt with by the police, so did not take part in the survey.

NB: The prevalence values for named drugs refer to the occurrence of those drugs alone; combinations of drugs are given separately.

Large differences were observed among the EU countries. The prevalence of alcohol was highest in the southern European countries and in Belgium. The prevalence of illicit drugs was highest in the southern European countries. The prevalence of medicinal drugs was highest in northern European countries. The prevalence of alcohol and drugs in eastern European countries was often much lower than in the rest of Europe.

In addition to the DRUID roadside survey, nine other surveys were identified, some of which originated from developing countries including Brazil, China and Thailand (Table A2).

In the United States, the 2007 National Roadside Survey (Lacey et al., 2011) was a large national field survey of alcohol- and drug-involved driving conducted primarily among night-time weekend drivers, but also daytime Friday drivers. The survey involved randomly stopping drivers at 300 locations across the continental United States; sites were selected through a stratified random

sampling procedure. This included data that were collected during a 2-hour Friday daytime session at 60 locations and during four 2-hour night-time periods (10.00 p.m. to midnight and 1.00 a.m. to 3.00 a.m. on both Friday and Saturday) at 240 locations.

It is difficult to compare the results of the different studies because of the many differences in methodology (see Chapter 1), including sampling during the whole week or only at the weekends, type of biological fluid, analytical methods and cut-offs, and reporting (global data or data broken down by sex, total prevalence of all drugs combined or prevalence of individual drugs, etc.). There are, however, some similarities. Higher percentages of drug- and alcohol-positive drivers are observed in studies that were performed only at the weekends or at night. In studies that cover the whole driving population, between 4 % and 6 % are drug and/or alcohol positive. In truck drivers in Brazil one finds mainly stimulant drugs (Leyton et al., 2012), while in Norway the percentage of drug-positive drivers is much lower (Gjerde et al., 2012). In the US and Canadian studies, sampling took place mainly at the weekends and at night, and the percentage of drug-positive drivers was 12–15 %, double the percentage in Europe. In the United States, cannabis was by far the most prevalent drug. In Australia (Davey and Freeman, 2009), methamphetamine and MDMA were most prevalent.

The data in Table A2 (Appendix) also show that a combination of alcohol and drugs is found in about 0.4–3.4 % of the general driving population. Combinations of different drug classes were observed in 0.2–2.3 % of drivers.

Subsets of drivers

Drivers injured in traffic accidents

Table A3 (Appendix) shows the results of the DRUID study in severely injured drivers. The percentage of drivers who tested positive for at least one psychoactive substance ranged from 28 % (Lithuania) to 53 % (Belgium). Alcohol (≥ 0.1 g/l) was the most common substance, with the highest percentage in Belgium (42.5 %), followed by Finland (32.1 %). Among the alcohol-positive drivers, 90.5 % had a blood alcohol concentration (BAC) ≥ 0.5 g/l and 65.7 % had a BAC ≥ 1.3 g/l. Benzodiazepines (0.0–10.2 %) and medicinal opioids (0.5–7.8 %) were the most prevalent medicinal drugs, but in half of cases the concentrations were lower than therapeutic. Cannabis (0.5–7.6 %) and amphetamines (0.1–4.2 %) were the most prevalent illicit drugs. The prevalence of Z-hypnotics and medicinal opioids ranged from 0 % to 3.8 % and from 1.1 % to 13.0 %, respectively. The prevalence of illicit drugs ranged from 2.3 % to 12.6 %. Alcohol was found in combination with drugs in 2.3–13.2 % of drivers. Drug combinations were found in 0.5–4.3 % of drivers (Legrand et al., 2012).

Table A4 (Appendix) compares 12 other (non-DRUID) studies on drug prevalence in injured drivers published since 2007: two from Australia, Brazil and Italy and one each from Greece, Hong Kong, the Netherlands, Norway, Spain and Sweden.

Drugs and/or alcohol were frequently detected in injured drivers (between 10 % and 44 %), much more frequently than in the general driving population. Alcohol was detected in 7–31 % of injured drivers, illicit drugs in 4–12.5 % and medicinal drugs in 13–21 % (not all drug classes were measured in all the studies). In 8 of the 12 studies, cannabis was the most frequently detected drug. However, in Norway (Bogstrand et al., 2011) and Sweden (Ahlm et al., 2009), benzodiazepines were the most frequently detected drugs, while ketamine was the most frequently detected drug in Hong Kong (Wong et al., 2010) and cocaine was the most frequently detected drug in one of the Italian studies (Siliquini et al., 2007).

The combination of alcohol and drugs was also frequently encountered, with prevalence ranging from 2 % to almost 12 %. Combinations of different drug classes were observed in 3.0–9.4 % of injured drivers.

There is a large variation in the percentages of drug-positive samples in the different studies, but this is probably because of the differences in methodology and study location (see Chapter 1).

Drivers killed in traffic accidents

The results of recent epidemiological studies that investigated the presence of alcohol, drugs and/or medicines in drivers who were killed in traffic accidents are given in Table A5 (Appendix) for the DRUID studies and in Table A6 for the other studies.

The DRUID project investigated the presence of alcohol and drugs in killed drivers in four countries: Portugal, Finland, Sweden and Norway (Legrand et al., 2014). The prevalence of any psychoactive substance ranged between 31 % and 48 %. Alcohol (≥ 0.1 g/l) was the

most common finding; 87 % had a BAC ≥ 0.5 g/l. Benzodiazepines (1.8–13.3 %) and amphetamines (0–7.4 %) were the most prevalent psychoactive medicines and illicit drugs, respectively. Alcohol–drug and drug–drug combinations were also common.

Nine other studies have been published since 2007: some of them are very large studies, involving more than 5 000 killed drivers in the United States (Brady and Li, 2013), France (Biecheler et al., 2008) and Canada (Beasley et al., 2011). The other studies were performed in the Nordic countries (Morland et al., 2011), Norway (Gjerde et al., 2011), Sweden (Ahlm et al., 2009; Jones et al., 2009), the United Kingdom (Elliott et al., 2009) and Portugal (Costa et al., 2012).

Alcohol was the most frequently detected psychoactive substance in drivers killed in accidents (25–40 %). However, drugs were also frequently detected, and, just as in injured drivers, at a much higher prevalence than among the general driving population. The combination of alcohol and drugs was also found in a substantial proportion of samples, ranging from 3.0 % to 26 %. In four studies, cannabis was the most commonly detected drug, with the highest prevalence, about 35 %, found in the United Kingdom. In the other studies, benzodiazepines were the most prevalent drug in Canada and Norway, opioids were the most prevalent in Portugal and antidepressants were the most prevalent in the study in the United Kingdom (Elliott et al., 2009).

Drivers suspected of driving under the influence of drugs and alcohol

Table A7 (Appendix) shows seven studies published since 2007 of drivers stopped on suspicion of drug use, from Australia (Chu et al., 2012), Canada (Palmentier et al., 2009), Austria (Keller et al., 2009), Denmark (Steentoft et al., 2010), Hungary (Toth et al., 2009), Sweden (Holmgren et al., 2007) and Switzerland (Senna et al., 2010).

The studies show a large variation in the number of drug-positive samples found on suspicion (80–96 %). This reflects differences in methodology, but also differences in procedures used to detect drivers who may be under the influence of drugs (see Chapter 1).

Ojaniemie et al. (2009) examined the main drug findings and their trends in suspected cases of driving under the influence of drugs in Finland. A register-based study was conducted of all suspected cases of driving under the influence of drugs during 1977–2007. The data included 31 963 offenders apprehended by the police with a positive finding for illicit/licit drug impairing driving performance. Toxicological results were analysed in blood and/or urine specimens in one central laboratory. The incidence of suspected cases of driving under the influence of drugs increased 18-fold during 1977–2007. Most of the suspects (89.7 %) were men. However, the male–female ratio decreased over the period from 13.9 to 7.3. The mean age decreased from 36.2 years in 1977 to 29.9 years in 2001, but then increased again. The substances found most often were benzodiazepines (75.7 %), amphetamines (46.0 %), cannabinoids (27.7 %) and opioids (13.8 %). The most common illicit drugs, amphetamines and cannabinoids, started to appear at the end of the 1980s. Polydrug findings were common (77.1 %). The number of cases suspected of driving under the influence of drugs have increased sharply since the introduction of a zero tolerance law, especially in regard to amphetamines.

Christophersen and Morland (2008) reported that drivers in Norway in whom benzodiazepines are detected are probably not representative of patients with benzodiazepine prescriptions. In the majority of benzodiazepine-positive drivers in their study, benzodiazepines were detected at supratherapeutic blood concentrations, and frequently in combination with illegal drugs, other psychoactive medicines or alcohol. Benzodiazepines were found to be the only drug present at therapeutic blood levels in less than 5 % of positive drivers (with the exception of nitrazepam, which was the only drug in 7.6 % of the drivers in whom it was detected). The majority of the drivers testing positive for benzodiazepines were 20–39 years old (median age for the different benzodiazepines 29–33 years), while the majority of those in whom benzodiazepines had been prescribed were over 50 years old.

Occurrence of new psychoactive substances in drivers

As many countries that wish to introduce legislation on driving under the influence are faced with the question of whether or not to include new psychoactive substances, we surveyed the literature for studies that had included new psychoactive substances. The results can be seen in Table 3. All studies were performed in drivers who were suspected of driving under the influence of drugs.

TABLE 3

Overview of the prevalence of some new synthetic drugs in drivers suspected of driving under the influence of drugs

Drug	Country	Year	Percentage/number	Reference
Desoxypipradol (2-DPMP)	Finland	2010–2012	1.7 %	Kriikku et al. (2013)
Fluoroamphetamines	Denmark	2009–2011	15 cases	Johansen and Hansen (2012)
GHB	Germany		2.0 %	Dresen et al. (2007)
GHB	Germany		2.0 %	Lott et al. (2012)
GHB	Norway	2000–2007	25 cases	Al-Samarraie et al. (2010)
GHB	Sweden	1998–2007	548	Jones et al. (2008a)
MDPV	Finland	2009	5.7 %	Kriikku et al. (2011)
Phenazepam	Finland	2010–2011	3.5 %	Kriikku et al. (2012)
Synthetic cannabinoids	Norway	2011	3 %. All samples contained other drugs as well	Bachs et al. (2012)

Abbreviations: GHB, gamma-hydroxybutyrate; MDPV, methylenedioxypyrovalerone.

Conclusion

In Europe, the United States, Australia and Canada, about 2–7 % of drivers stopped during roadside surveys tested positive for drugs or alcohol in blood or saliva. In the DRUID study, 7.43 % of the drivers tested positive for alcohol or one of the 23 tested drugs in their oral fluid or blood. Alcohol levels above 0.1 g/l and above 0.5 g/l were found in 3.5 % and 1.5 % of drivers, respectively. Regarding drugs, 1.9 % tested positive for illicit drugs, mainly cannabis, 1.4 % for (a limited list) of medicinal drugs, 0.37 % for a combination of alcohol and drugs and 0.39 % for different drug classes. Not unexpectedly, higher prevalence rates were found in studies using urine samples (9–10 %) and in studies in which samples were collected only on weekend nights (10–12 %). Studies conducted among drivers stopped on suspicion of alcohol or drug use or other subsets of drivers usually find a much higher prevalence rate (50–90 %) of drugs than roadside surveys of general driving populations, because of the selection bias inherent in such subset surveys.

In the DRUID project, the percentage of seriously injured drivers testing positive for at least one psychoactive substance ranged between 28 % and 53 %, with alcohol (≥ 0.1 g/l) being the most common substance. Among the alcohol-positive drivers, 90.5 % had a BAC ≥ 0.5 g/l and 65.7 % had a BAC ≥ 1.3 g/l. The prevalence of illicit drugs ranged between 2.3 % and 12.6 %. Alcohol was found in combination with drugs in 2.3–13.2 % of the drivers. Drug combinations were found in 0.5–4.3 % of the drivers in DRUID and in an even higher percentage (3.0–9.4 %) in the other studies. In the other studies of injured drivers, drugs and/or alcohol were frequently detected (between 10 % and 44 %). In 8 of the 12 studies, cannabis was the most frequently detected drug.

In killed drivers, the prevalence of any psychoactive substance ranged between 26 % and 57 %. Alcohol (≥ 0.1 g/l) was the most common finding; between 19 % and 45 % of drivers tested positive. In the DRUID survey, 87 % had a BAC ≥ 0.5 g/l. In the DRUID survey, benzodiazepines (1.8–13.3 %) and amphetamines (0–7.4 %) were the most prevalent psychoactive medicines and illicit drugs, respectively. In four studies, cannabis was the most commonly detected drug, with the highest prevalence, about 35 %, being found in the United Kingdom. The combination of alcohol and drugs was also frequent in a substantial proportion of samples, ranging from 3.0 % to 26 %.

In studies carried out in drivers stopped on suspicion of driving under the influence of drugs, a psychoactive substance other than alcohol is often detected in more than 80 % of the samples; in most studies, it is cannabis. Drivers suspected of driving under the influence of alcohol are frequently also under the influence of drugs. In nearly all studies cannabis was the most frequently detected drug, except in Sweden (amphetamines) and Denmark (benzodiazepines). Some studies also looked for new synthetic drugs and found them in up to 6 % of drivers suspected of driving under the influence.

The comparability of these prevalence studies is low. For future research, comparability may be improved if certain minimum common standards are adopted. Nevertheless, from the studies that have been published since 2007, it can be concluded that driving under the influence of drugs is not uncommon and that it can cause substantial risk to road users.

3

CHAPTER 3
Effects and risks associated with drugs

For each type of drug considered, the effects on performance that have been assessed by experimental studies will be described. These effects are mostly divided into acute and chronic effects. Acute effects are the effects associated with the use of a single dose of a drug. Chronic effects are the effects of using a specific drug over a long period of time. Where possible, data on the risks associated with these drugs in traffic will also be described.

Cannabis

Acute effects

The effects of cannabis vary with dose, route of administration, experience of the user, vulnerability to psychoactive effects and setting of use. Cannabis can produce euphoria, relief of anxiety, sedation and drowsiness. Occasionally, the use of cannabis can cause anxiety that may escalate to panic attacks and paranoia. A sense of enhanced well-being may alternate with a depressive phase (Huestis, 2002). Users are aware of the effects of the drug, and this awareness increases with higher doses (Lane et al., 2005; Liguori et al., 2002; Menetrey et al., 2005; Sexton et al., 2000). Cannabis can also cause some physiological effects such as mydriasis (Sexton et al., 2000).

Cannabis acutely reduces some cognitive and psychomotor skills that are necessary to drive, such as motor control, psychomotor speed, executive function, motor impulsivity, visual processing, short-term memory, working memory (reaction time and accuracy), perception and balance, and these effects are mostly dose dependent (Hart et al., 2001; Ilan et al., 2004; Kurzthaler et al., 1999; Liguori et al., 2002; Menetrey et al., 2005; Nicholson et al., 2004; Ramaekers et al., 2006a; Sexton et al., 2000). Using driving simulator tests, Menetrey et al. (2005) found that keeping a vehicle on a track is the most difficult task for participants under the influence of cannabis. Liguori et al. (2002) found a significant effect of cannabis on body sway, but no effect on brake latency. In agreement with these results, Sexton et al. (2000) showed that the SDLP in the road-tracking test was the most sensitive measure for revealing the adverse effects of THC.

Pharmacology of cannabis

Cannabis is a natural product, the main psychoactive constituent of which is tetrahydrocannabinol (THC). The cannabis plant (*Cannabis sativa* L.) is broadly distributed and grows in temperate and tropical areas. Cannabis resin is a compressed solid made from the resinous parts of the plant, and cannabis (hash) oil is a solvent extract of cannabis.

The pharmacology of cannabis is complicated by the presence of a wide range of cannabinoids. Anandamide has been identified as the endogenous ligand for the cannabinoid receptor and has pharmacological properties similar to those of THC. When cannabis is smoked, THC can be detected in plasma within seconds of inhalation; it has a half-life of 2 hours. Following smoking of the equivalent of 10–15 mg over a period of 5–7 minutes, peak plasma levels of THC are around 100 µg/l. It is highly lipophilic and widely distributed in the body. Two active metabolites are formed: 11-hydroxy-Δ^9-THC and 8β-hydroxy-Δ9-THC. The first is further metabolised to Δ^9-THC-11-oic acid. Two inactive substances are also formed (8α-hydroxy-Δ^9-THC and 8α,11-dihydroxy-Δ^9-THC) as are many other minor metabolites, most of which appear in the urine and faeces as glucuronide conjugates. Some metabolites can be detected in the urine for up to 2 weeks following smoking or ingestion.

Source: EMCDDA drug profiles (http://www.emcdda.europa.eu/publications/drug-profiles).

Cannabis can also have an effect on behaviour. The effect of cannabis on risk taking is, however, unclear. Laboratory experiments revealed an increased impulsive response in the stop signal task, indicating that the subjects were unable to inhibit a response in a rapid response model while under the influence of cannabis (McDonald et al., 2003; Ramaekers et al., 2006a). Lane et al. (2005) found that, when subjects were presented with a choice between two response options operationally defined as risky and non-risky, cannabis increased selection of the risky option. However, performance on other behavioural measures of impulsivity (go/no go, Iowa gambling task) was not affected (McDonald et al., 2003; Ramaekers et al., 2006a). In some driving studies that used low doses of cannabis, it was observed that the subjects were aware of the impairment and compensated for their driving style by driving more slowly, overtaking less or keeping longer distances. However, they were still unable to compensate for the loss of capability in some psychomotor skills (Sexton et al., 2000, 2002). Experimental studies on cannabis have traditionally used low-potency cannabis (maximum 4 % THC). Other studies that have used high-potency cannabis (13 % THC) have found that impairment is more pronounced than in the low-potency studies (see Chapter 1).

In an interesting study that gives us some clues about the impairing effect of cannabis on brain mechanisms, Battistella et al. (2013) evaluated the impact of cannabis on the driving ability of occasional smokers by investigating changes in the brain network involved in a tracking task. Thirty-one male volunteers were enrolled in a study that included functional magnetic resonance imaging (fMRI) of the brain and measurements of psychomotor skills. Cannabis smoking (42 mg of THC), even at low THC blood concentrations, decreased psychomotor skills and altered the activity of the brain networks involved in cognition. After cannabis smoking, blood oxygen level-dependent response decreased in the anterior insula, dorsomedial thalamus and striatum, suggesting an alteration of the network involved in saliency detection. In addition, the decrease in blood oxygen level-dependent response in the right superior parietal cortex and in the dorsolateral prefrontal cortex indicated the involvement of the control executive network known to operate once the saliencies are identified. Furthermore, cannabis increased activity in the rostral anterior cingulate cortex and ventromedial prefrontal cortices, suggesting an increase in self-orientated mental activity. Subjects were more attracted by intrapersonal stimuli ('self') and failed to attend to task performance, leading to an insufficient allocation of task-orientated resources and suboptimal performance. These effects correlated with the subjective feeling of confusion rather than with the blood concentration of THC.

Bosker et al. (2012a) measured the acute and chronic effects of dronabinol (medicinal THC) on actual driving performance and the standard field sobriety test (SFST) in 12 occasional and 12 heavy cannabis users who received single doses of placebo, 10 mg dronabinol or 20 mg dronabinol. SDLP ($p = 0.008$) in occasional users increased after dronabinol administration. Dronabinol-induced impairment, reflected in increments in SDLP, was greater than impairment associated with a BAC of 0.5 g/l in occasional and heavy users, although the magnitude of driving impairment was generally smaller in heavy users. Levels of the subjective 'high' feeling were comparable in occasional and heavy users. Dronabinol impaired driving performance in occasional and heavy users in a dose-dependent way, but to a lesser degree in heavy users, possibly because of tolerance. The SFST was not sensitive to clinically relevant driving impairment caused by oral tetrahydrocannabinol.

Lenné et al. (2010) compared the effects of three doses of cannabis and alcohol (placebo, low and high doses; 0, 0.4 and 0.6 g/kg), both alone and in combination, on driving performance. The driving performance of 25 experienced and 22 inexperienced drivers was tested in a simulator under nine different drug conditions. The simulator replicated the driving environment found on a main urban road, and during the test workload was varied through both the drive characteristics and the inclusion of a secondary task. High levels of cannabis generally induced greater impairment than lower levels, while alcohol at the doses used had few effects and did not produce synergistic effects when combined with cannabis. Both cannabis and alcohol were associated with increases in speed and lateral position variability: high-dose cannabis was associated with decreased mean speed, increased mean headway and increased headway variability, and a longer reaction time, whereas alcohol was associated with a slight increase in mean speed.

Mann et al. (2007) examined self-reported collision involvement in the last 12 months by lifetime use of cannabis, past-year use of cannabis and past-year driving after using cannabis, while controlling for demographic characteristics, and found that the odds of reporting collision involvement was significantly higher among cannabis users and among those who reported driving after cannabis use. Some evidence of a dose–response relationship was also seen. In a more recent study (Mann et al., 2010), several demographic factors were found to be significantly associated with self-

reported collision involvement. The logistic regression model revealed that age, region, income, marital status and number of kilometres driven in a typical week were all significantly related to collision involvement, after adjusting for other factors. Respondents who reported having driven after cannabis use within the past 12 months had an increased risk of collision involvement (OR 1.84) than those who never drove after using cannabis, and this increase was of a greater magnitude than that associated with having reported driving after drinking within the past 12 months (OR 1.34).

Weinstein et al. (2008a) investigated the acute effects of 13 mg and 17 mg THC on skills important for coordinated movement and driving and on subjective and autonomic measures in 14 regular users of marijuana. Regular marijuana users hit the walls on the virtual maze task more often after smoking a cigarette containing 17 mg THC than after smoking cigarettes without THC. This effect was not seen in subjects after they smoked cigarettes containing 13 mg THC. Performance on the WCST was also affected by 17 mg THC and, to a lesser extent, by the use of 13 mg THC. Decision-making in the gambling task was affected after smoking cigarettes with 17 mg THC, but not 13 mg THC. These findings imply that smoking of 17 mg THC results in impairment of cognitive–motor skills that could be important for coordinated movement and driving, whereas the lower dose of 13 mg THC appears to cause less impairment of such skills in regular users of marijuana. In another study from the same group (Weinstein et al., 2008b), 12 regular users of marijuana underwent two positron emission tomography (PET) scans using [^{18}F]-fluorodeoxyglucose, one while subject to the effects of 17 mg THC, the other without THC. In both sessions, a virtual reality maze task was performed during the fluorodeoxyglucose uptake period. Again, regular marijuana smokers more often hit the walls on the virtual maze task when subject to the effects of 17 mg THC than without THC. Compared with results without THC, 17 mg THC increased brain metabolism during task performance in areas that are associated with motor coordination and attention in the middle and medial frontal cortices and anterior cingulate, and reduced metabolism in areas that are related to visual integration of motion in the occipital lobes.

Khiabani et al. (2008) found that a substantial fraction of Δ^9-THC-positive drivers were tachycardic, but there was no correlation between blood Δ^9-THC concentration and pulse rate. Without further diagnostic information on the cause of the pulse irregularities, their results indicate that occasional users of cannabis tend to have irregular heart rates at low THC concentrations and at low pulse rates.

In a review in the *Lancet* (Hall and Degenhardt, 2009), focusing on adverse health effects of the greatest potential public health interest (those that are most likely to occur and to affect a large number of cannabis users), the most probable adverse effects included a dependence syndrome, increased risk of motor vehicle crashes, impaired respiratory function, cardiovascular disease and adverse effects of regular use on adolescent psychosocial development and mental health. In a review of the effects of cannabis on driving, Hartman and Huestis (2013) found that, historically, delays in sample collection, evaluating the inactive THC metabolite 11-nor-9-carboxy-THC and polydrug use have complicated epidemiological evaluations of driver impairment after cannabis use. Epidemiological data show that the risk of involvement in a motor vehicle accident (MVA) increases approximately twofold after cannabis smoking. The adjusted risk of driver culpability also increases substantially, particularly with increased blood concentrations of THC. Experimental data show that drivers attempt to compensate by driving more slowly after smoking cannabis, but control deteriorates with increasing task complexity. Cannabis smoking increases lane weaving and impaired cognitive function. Reaction times, performance on CTTs and divided attention tasks and maintenance of lane position are all impaired by cannabis. Despite purported tolerance in frequent smokers, performance of complex tasks still shows impairment.

The dose–effect relationship between the THC dose contained in cannabis cigarettes and cognitive and psychomotor effects for THC doses up to 69.4 mg (23 %) were studied in a double-blind, placebo-controlled, randomised, four-way crossover study of 24 male non-daily cannabis users. Participants smoked four cannabis cigarettes containing 0, 29.3, 49.1 and 69.4 mg THC on four exposure days. The THC dose in smoked cannabis was linearly associated with a slower response time on all tasks (SRT, visuospatial selective attention, sustained attention, divided attention and short-term memory tasks) and with motor control impairment in the motor control task. The number of errors on the short-term memory and the sustained attention tasks increased significantly with increasing doses. Some participants showed no impairment of motor control even at THC serum concentrations higher than 40 ng/ml. The 'high' feeling and drowsiness differed significantly between treatments (Hunault et al., 2009).

Meta-analysis of experimental studies

Berghaus et al. (2010) performed a meta-analysis of the experimental studies. For oral administration of THC, 21

studies measured 482 effects. The doses used varied from 7.5 to 39 mg. For the highest dose range (18–39 mg), the maximal percentage of significantly impaired test results was 55 %. The time to maximal impairment varied from 2.25 hours to 1 hour with increasing doses. The alcohol equivalence of maximum impairment was < 0.3 g/l for a dose lower than 9 mg, over 0.5–0.8 g/l for 9–18 mg and > 0.8 g/l for a dose > 18 mg. The duration of impairment was about 5 hours at the middle dose range. The 0.5 g/l BAC equivalent THC concentration was 3.7 ng/ml in plasma. For smoking of cannabis, 78 studies with 888 effects were analysed. The doses used varied between 1 and 52 mg. For the highest dose range (18–52 mg), the maximal percentage of significantly impaired test results was 55 %. The time to maximal impairment varied from 0.75 hours to 0.25 hours with increasing doses. The alcohol equivalence of maximum impairment was 0.8 g/l or higher at all doses. The duration of impairment was about 4.75 hours for the middle dose range. The 0.5 g/l BAC equivalent concentration was 3.8 ng/ml in plasma.

Duration of effects

The desired effect of cannabis, the 'high', lasts for up to 2 hours (Couper and Logan, 2004a). However, most studies found significant negative effects of cannabis on performance up to 10 hours after use (Hart et al., 2001; Kurzthaler et al., 1999; Lane et al., 2005; McDonald et al., 2003; Menetrey et al., 2005; Ramaekers et al., 2006a). Nicholson et al. (2004), for example, found that memory was impaired in healthy volunteers 10 hours after administration of 15 mg of THC.

Combination with other psychoactive substances

Some deleterious effects of cannabis appear to be additive or even synergistic with those of alcohol; the combination of both substances results in a prolongation as well as enhancement of their effects (Baselt, 2001). For example, stronger subjective effects are generated after the use of a combination of alcohol and cannabis than after the use of either substance alone (Sexton et al., 2002). Driving studies show that drivers under the influence of both alcohol and cannabis are less attentive to traffic approaching from side streets, while the use of either cannabis or alcohol has no effect (Lamers and Ramaekers, 2001), and that the combination of cannabis and alcohol generates an additional decrement in lateral control on top of the decrement caused by either cannabis or alcohol (Sexton et al., 2002). Liguori et al. (2002), however, found no additive effects of alcohol and cannabis on brake latency or body sway.

In an analysis of the SAM study of fatal crashes in France, Biecheler et al. (2008) found that about 40 % of drivers under the influence of cannabis also had an illegal alcohol level. The ratio of responsible to not responsible drivers was 1.2 in the alcohol- and drug-free population, 2.3 in the cannabis-only population (THC ≥ 1 ng/ml), 9.4 in the alcohol-only population (≥ 0.5 mg/l) and 14.1 in the alcohol–cannabis combination population.

Lenné et al. (2010) found that alcohol at the doses used (up to 0.6 g/kg) did not produce synergistic effects when combined with cannabis.

Ronen et al. (2010) investigated the effect of alcohol (BAC = 0.05 %) and THC (13 mg) and their combination on driving and non-driving tasks, and willingness to drive based on subjective sensations and the perceived effects of the drugs, in seven healthy men and five healthy women, aged 24–29 years, all of whom were recreational users of alcohol and marijuana. Overall, the combination of alcohol and THC had the greatest effect as determined by impaired performance on the driving and non-driving tasks, subjective sensations after intake and physiological measures. Despite significant differences in the size of the effects after the various treatments, there were no differences in the distances subjects were willing to drive while under the influence of each of the treatments. No residual effects were observed after 24 hours.

In another responsibility analysis in France Gadegbeku et al. (2011) found no interaction between cannabis and alcohol intoxication ($p = 0.13$), 'only' a multiplicative effect. The OR of responsibility for a fatal crash when under the influence of both alcohol and cannabis (compared with drivers not exposed to cannabis or alcohol) was estimated at 15.86 (8.39 × 1.89). Lenguerrand et al. (2008), based on the same data, came to the same conclusions: the risk of causing a crash for those under the influence of alcohol and cannabis while driving (OR 14.2) was similar to the product of the adjusted individual effects. Hartman and Huestis (2013) found that combining cannabis with alcohol increases impairment, especially lane weaving.

Downey et al. (2013) assessed performance on a driving simulator in 49 men and 31 women, previous recreational users of alcohol and marijuana, who were abstinent at the time of the experiment. In six experimental sessions, participants consumed cigarettes containing no THC, 1.8 % THC or 3 % THC together with alcohol to achieve a BAC of 0 %, 0.03 % or 0.05 %. Half of the participants were allocated to the cannabis with no and low alcohol (0.03 % BAC) group,

and the other 40 participants were allocated to the cannabis with no and high alcohol (0.05 % BAC) group. The level of THC detected in blood was higher when THC was consumed with alcohol than when cannabis was consumed alone, and regular cannabis users returned higher levels of THC in plasma than non-regular users. Performance on the simulator was more impaired when THC and alcohol were combined. Generally, regular cannabis users displayed more driving errors than non-regular cannabis users.

Romano and Voas (2011) found a link between drug consumption and fatal crashes, but the contribution of the different drug classes involved varied depending on the cause of the crash (speeding, failure to obey/yield, inattention) and use or not of a seatbelt. Of the two drug classes most commonly used, stimulants more than cannabinoids were found to be associated with all four categories of crashes under study. The contribution of drugs to fatal crashes is important mainly in the absence of an impairing level of alcohol. When drivers are alcohol impaired, the influence of other drugs is less significant. Counter to the commonly held belief, no synergistic drugs–alcohol effect was found. Rather, it appeared that, when present, alcohol was the main source of impairment. The study raises some interesting questions regarding the way drugs contribute, and sometimes in unexpected ways, to crashes, as the effects of drug consumption were found to vary depending on the type of crash considered, the class of drug and the presence of alcohol.

Sewell et al. (2009) reviewed the literature on cannabis, alcohol and driving and concluded that cannabis and alcohol acutely impair several driving-related skills in a dose-related fashion, but the effects of cannabis vary more between individuals than do the effects of alcohol because of tolerance, differences in smoking technique and different absorptions of THC. The detrimental effects of cannabis use vary in a dose-related fashion, and highly automatic driving functions are more severely impaired than more complex tasks that require conscious control; alcohol, in contrast, causes greater impairment of consciously performed tasks than of automatic tasks. For this reason, and because they have greater awareness of their impairment, marijuana smokers tend to compensate effectively while driving by utilising a variety of behavioural strategies. However, concomitant consumption of alcohol eliminates the ability to use such strategies effectively and results in impairment even at doses which, were they of either drug alone, would be insignificant.

Chronic effects

Chronic use of cannabis can lead to deficiencies in memory, attention, manual dexterity, executive functioning and psychomotor speed (Bolla et al., 2002; Ehrenreich et al., 1999; Pope et al., 2001; Solowij et al., 2002). These effects can last longer than the period of intoxication and worsen with either increasing number of years or frequency of cannabis use. The defects are partially reversible with prolonged abstinence, but some impairment may be permanent. In particular, Bolla et al. (2002) showed that very heavy use of marijuana is associated with persistent decrements in neurocognitive performance even after 28 days of abstinence. Pillay et al. (2008) performed fMRI studies on 11 cannabis users and 16 comparison subjects for up to 28 days of abstinence from cannabis, and demonstrated that 28 days may not be a sufficient washout period for chronic cannabis users to be ensured optimal motor planning and execution, as reflected by diminished supplementary motor cortex activation as long as 28 days after discontinuation. Very recently, Bosker et al. (2013) assessed performance on the CTT and divided attention task in 19 male chronic, daily cannabis smokers at baseline and after 8, 14–16 and 21–23 days of continuously monitored abstinence. Psychomotor performance was compared with that of a control group of non-intoxicated occasional drug users. Sustained cannabis abstinence moderately improved cannabis smokers' performance of both CTTs and the divided attention task, but even after 3 weeks of abstinence performance was impaired compared with that of control subjects. Thirty-three per cent of the daily cannabis smokers had no THC in their blood 3 weeks after stopping, and the mean THC, 11-OH-THC and THC-COOH concentrations were 0.4, 0.0 and 2.2 ng/ml, respectively. The authors cautioned that between-group differences need to be interpreted with caution as chronic smokers and control subjects were not matched for education, socioeconomic status, lifestyle or race.

Threshold concentration

Ramaekers et al. (2006b) measured performance impairment (in terms of motor control, motor impulsivity and executive function) as a function of THC concentration in serum and oral fluid and concluded that impairment of performance first occurs at a serum THC concentration between 2 and 5 ng/ml. Binomial tests showed an initial and significant shift towards impairment of performance on the CTT at serum THC concentrations between 2 and 5 ng/ml. At concentrations between 5 and 10 ng/ml, approximately 75–90 % of the observations were indicative of

significant impairment in every performance test. At THC concentrations above 30 ng/ml, 100 % of observations in every performance test were indicative of significant impairment. According to Mura et al. (2005), cannabis can be detected in those regions of the brain on which it has an influence even after it is no longer detectable in blood. In the DRUID meta-analysis, a level of 3.8 (3.3–4.1) ng/ml of THC in plasma has similar effects to 0.5 g/l of alcohol.

According to Grotenhermen et al. (2007), based on a small number of epidemiological studies, serum concentrations of THC below 10 ng/ml are not associated with an elevated accident risk. A comparison of meta-analyses of experimental studies on the impairment of driving-relevant skills by alcohol or cannabis suggests that a serum THC concentration of 7–10 ng/ml is associated with an impairment comparable to that caused by a BAC of 0.5 g/l. Thus, a suitable numerical limit for THC in serum may fall in that range. Other authors suggest much lower cut-off concentrations. Battistella et al.'s (2013) findings that the effects correlate with the subjective feeling of confusion rather than with the blood level of THC lend support for the zero-tolerance policy adopted in several countries that prohibits the presence of any amount of drugs in blood while driving.

In epidemiological studies, an increased accident risk was observed at THC concentrations above 2 ng/ml (Kuypers et al., 2012; Laumon et al., 2005) or even 1 ng/ml (Gadegbeku et al., 2011) in whole blood. Hartman and Huestis (2013) found evidence that suggested that recent cannabis smoking and/or blood THC concentrations of 2–5 ng/ml are associated with substantial driving impairment, particularly in occasional smokers.

Jones et al. (2008b) studied THC concentrations in 8 794 cases of suspected DUI in Sweden and concluded that the concentration of THC in blood at the time of driving is probably a great deal higher than at the time of sampling (30–90 minutes later). Imposing limits on the concentration of THC in blood based on the results of scientific studies (e.g. 3–5 ng/ml), as discussed in some quarters, would result in many individuals evading prosecution. Zero tolerance or limit of quantitation laws are a much more pragmatic way to enforce legislation on driving under the influence of drugs.

Karschner et al. (2009a) found substantial whole-blood THC concentrations 7 days after drug discontinuation in heavy chronic cannabis users. In another study (Karschner et al., 2009b), plasma cannabinoid concentrations were determined in 18 long-term heavy cannabis smokers in an in-patient research unit during a 7-day period of monitored abstinence. THC concentrations were > 1 ng/ml (1.2–5.5 ng/ml) in nine (50.0 %) participants on abstinence day 7. Measurable THC concentrations after 7 days of abstinence indicate a potential mechanism for the residual neurocognitive impairment observed in chronic cannabis users. The presence of THC in plasma after 7 days of abstinence suggests that its detection may not indicate recent use in daily cannabis users. These findings may also impact on the implementation of per se limits in legislation on driving under the influence of drugs.

An expert panel in Norway (Vindenes et al., 2012) proposed that, for the purpose of imposing sanctions, cut-off values for THC in blood of 1.3, 3.0 and 9.0 ng/ml should be considered equivalent to alcohol levels of 0.2, 0.5 and 1.2 g/l, respectively.

Risks

When studying the risks associated with cannabis use, the results can be misleading if samples are analysed for THC-COOH, as this is an inactive metabolite of cannabis that can be present in blood or urine even though the subject is no longer impaired. Better correlation with impairment can be achieved by testing for THC, the primary active ingredient of cannabis (Verstraete, 2004).

Accident risk

Four epidemiological studies investigated the risk of being involved in a traffic accident while driving under the influence of cannabis. A case–control study in Québec, Canada, found that driving under the influence of cannabis alone was associated with an OR of 2.2 (95 % CI 1.5–3.4); however, taking account of all cannabis cases resulted in an OR of 4.6 (95 % CI 3.4–6.2) (Dussault et al., 2002). Driving under the influence of a combination of alcohol (BAC > 0.8 g/l) and cannabis was associated with an increased accident risk of 80.5 (OR; 95 % CI 28.2–230.2). In France, the prevalence of alcohol, cannabis and other drugs was compared in 900 injured drivers and 900 control subjects (Mura et al., 2003). Among drivers below the age of 27 years, driving under the influence of cannabis alone was associated with an increased accident risk of 2.5 (OR; 95 % CI 1.5–4.2); with alcohol (BAC > 0.5 g/l) plus cannabis the increased risk was 4.6 (OR; 95 % CI 2.0–10.7). The Impaired Motorists, Methods of Roadside Testing and Assessment for Licensing (Immortal) study in the Netherlands and Norway found an increased accident risk (albeit not statistically significant) for

driving under the influence of cannabis alone (Assum et al., 2005).

The accident risk associated with driving under the influence of cannabis has also been studied based on the results of surveys instead of detection procedures. Fergusson and Horwood (2001) examined associations between cannabis use and traffic accident risks in a birth cohort of 907 New Zealanders aged 18–21 years. They found statistically significant relationships between reported annual cannabis use and annual accident rates, but only for 'active' accidents in which the driver's behaviour contributed to the accident. Those using cannabis more than 50 times a year had estimated rates of active accidents that were 1.6 (95 % CI 1.2–2.0) times higher than for non-users. However, when driver behaviours and characteristics related to cannabis use were controlled for, no association between cannabis use and accident risks was apparent. These data thus suggest that cannabis use is associated with an increased risk of responsibility for an accident, but that this increased risk appears to reflect the characteristics of the young people who used cannabis rather than the effects of cannabis on driver performance.

Fergusson et al. (2008) examined the associations between driving under the influence of (a) cannabis and (b) alcohol and motor vehicle collisions in a longitudinal study of a New Zealand birth cohort (n = 936). Participants reported significantly ($p < 0.0001$) greater rates of driving under the influence of cannabis than driving under the influence of alcohol at the ages of 21–25 years. After adjustment for potentially confounding factors, the associations between driving under the influence of cannabis and motor vehicle collisions remained marginally significant ($p = 0.064$), whereas adjustment for confounding factors reduced the association between driving under the influence of alcohol and motor vehicle collisions to statistical non-significance ($p > 0.70$).

Gerberich et al. (2003) conducted a retrospective study in northern California among members of a large health insurance cohort who had completed baseline questionnaires about health behaviours, including cannabis use, and health status between 1979 and 1985. In addition, all subjects' hospitalisations for injuries until 31 December 1991 were identified. Statistical analysis showed a higher incidence of motor vehicle injuries in men who were current users of cannabis than in non-users. There were no differences among female cannabis users or former users.

In a case–control study, Blows et al. (2005) recorded drivers' self-reported cannabis use in the 3 hours prior to the crash (or, in the case of the control subjects, the 3 hours prior to the survey) and habitual cannabis use in the previous 12 months. The cases were drivers involved in crashes and the control group consisted of drivers in a random sample of cars. Acute cannabis use was significantly associated with car crash injury. However, after adjusting for confounders (BAC, seatbelt use, speed and sleepiness score), this effect was no longer significant. There was a strong significant association between habitual use and car crash injury, even after adjustment for all the above confounders plus acute use prior to driving (OR 9.5; 95 % CI 2.8–32.3).

Asbridge et al. (2005) questioned 6 087 senior students about driving under the influence of cannabis and involvement in motor vehicle collisions. Students who had driven under the influence of cannabis in the previous year were over four times as likely as cannabis-free drivers to have been involved in a motor vehicle collision, but those who used the drug but did not drive while they believed themselves to be under its influence did not experience more accidents.

A similar study was conducted among cannabis users in Australia (Jones et al., 2005). The likelihood of having had an accident in the previous year was 7.4 % for those who had not driven within an hour of using a drug in the previous 12 months and 10.7 % for those who reported driving after using cannabis only. The proportion who had had an accident in the previous year was much higher among those who reported driving after using cannabis with alcohol or other illicit drugs — either simultaneously (24 %) or on different occasions (23 %) — than it was for the other drivers.

Based on the DRUID results in Belgium (Kuypers et al., 2012), an OR of 12.10 (95 % CI 3.62–40.43, $p < 0.001$) was calculated. For THC concentrations of 1–1.99 ng/ml the OR was 5.84 (95 % CI 0.56–60.48, not statistically significant), for THC concentrations of 2–4.99 ng/ml the OR was 22.24 (95 % CI 2.38–207.77, $p = 0.007$) and for THC concentrations > 5 ng/ml the OR was 13.16 (95 % CI 1.90–91.18, $p = 0.009$). Evaluation of these results has shown that the OR might be spuriously elevated as a result of selection bias in the control group (Houwing et al., 2013).

Pulido et al. (2011a) calculated a RR of driving-related injury in the 60 minutes following cannabis use of 7.0 (95 % CI 3.1–16). This value increased to 11 (95 % CI 1.3–88) for concurrent exposure to alcohol and decreased to 6 (95 % CI 2.4–14) for non-concurrent exposure to any other psychoactive drug. The RRs were considerably lower when the hazard period was increased to 120 minutes. In another study by the same

group (Pulido et al., 2011b), logistic regression was used to adjust for distance driven and potential confounders among 17 484 car or motorcycle drivers in 2005 in Spain. Cannabis use on more than 4 days a week was associated with a higher number of traffic injuries.

Richer and Bergeron (2009) found that driving under the influence of cannabis is associated with self-reported and observed risky driving and negative emotional driving. They also found that sensation seeking and impulsivity are independent psychological predictors of driving under the influence of cannabis. Finally, a trend suggested that self-reported driving under the influence of cannabis is associated with an increased risk of being involved in a car accident, after controlling for dangerous driving and demographic variables.

In the United Kingdom, results from a postal questionnaire survey found that cannabis use was associated with an increased risk of road traffic accidents (OR 1.9; 95 % CI 1.0–3.5), and this risk increased with higher levels of other associated risk factors (Wadsworth et al., 2006).

In the DRUID case–control study (Hels et al., 2011), the RR of being seriously injured was estimated to be slightly increased (1–3). The adjusted OR, based on data for all countries, was 1.38 (95 % CI 0.88–2.17) for being seriously injured and 1.33 (95 % CI 0.48–3.67) for death.

Responsibility analyses

A study of 3 398 fatally injured drivers conducted in Australia from 1990 to 1999 found an OR of 2.7 (95 % CI 1.02–7.0) for responsibility for an accident while driving under the influence of cannabis alone (Drummer et al., 2004). For drivers with blood THC concentrations of 5 ng/ml or higher, the OR was greater and more statistically significant (OR 6.6, 95 % CI 1.5–28.0). A significantly stronger positive association with accident responsibility was seen in drivers who tested positive for cannabis and had a BAC of 0.5 g/l or higher compared with a BAC of 0.5 g/l or higher and no cannabis use (OR 2.9; 95 % CI 1.1–7.7). In another study in Australia, conducted in 1995–1996 and using blood samples from 2 500 injured drivers, no significant increase in responsibility (OR 0.8; 95 % CI 0.4–1.5) was found when cannabis was used alone (Longo et al., 2000b). The combination of alcohol and cannabis produced a significant increase in responsibility (OR 5.4; 95 % CI 1.2–24.0), but this increase was not significantly greater than that produced by alcohol alone. A responsibility analysis performed in Canada with 482 fatally injured drivers showed no statistically significant results for either cannabis alone (OR 1.2; 95 % CI 0.4–3.9) or the combination of alcohol (BAC > 0.8 g/l) and cannabis (OR 2.5; 95 % CI 0.3–20.2) (Dussault et al., 2002). Among 10 748 drivers involved in fatal crashes in France from October 2001 to September 2003, the presence of cannabis was associated with increased risk of responsibility (OR 3.3; 95 % CI 2.6–4.2) (Laumon et al., 2005). Moreover, a significant dose effect was identified, with OR increasing from 1.6 (95 % CI 0.8–3.0) for THC concentrations in blood of 0–1 ng/ml to 2.1 (95 % CI 1.3–3.4) for THC concentrations above 5 ng/ml. The effects of cannabis were adjusted for different co-factors, including BAC, age, vehicle type and time of crash. For driving under the influence of a combination of alcohol and cannabis, an OR of 14 (95 % CI 8.0–24.7) was calculated, which is very close to the value obtained from the product of the adjusted individual effects of alcohol and cannabis. In the United States, two analyses of injured drivers did not find an association between cannabis use and crash responsibility (Lowenstein and Koziol-McLain, 2001; Soderstrom et al., 2005). This may be the result of some methodological limitations, as both studies used urine for the toxicological analysis. As cannabis metabolites can be detected in urine for up to several days after chronic use, a sample testing positive for cannabis does not necessarily indicate recent use.

Lowenstein and Koziol-McLain (2001), however, performed secondary cannabis testing on the same urine samples by using a liquid–liquid extraction procedure that tests for the parent drug (THC) to differentiate between recent and non-recent use. Drivers were categorised as follows: acute cannabis use (THC positive), recent cannabis use (11-OH-THC positive) and remote cannabis use (THC-COOH positive). The researchers found no association between crash responsibility and acute cannabis use, nor between crash responsibility and recent cannabis use or remote cannabis use. However, the samples were frozen for up to one year; the freezing and thawing may have led to some degradation of the cannabis and possibly to an underestimation of the prevalence of acute and recent cannabis use.

In the Netherlands, Smink et al. (2005) investigated the relationship between cannabis use and the severity of a traffic accident in drivers involved in crashes from October 1998 to September 1999. Blood samples were screened for the presence of alcohol, illicit drugs and medicinal drugs. Logistic regression analysis showed no association between the use of cannabis and the severity of a traffic accident.

Gadegbeku et al. (2011) found that the effect of cannabis on fatal crash responsibility was significant

after adjustment for age, sex and alcohol level: the adjusted OR was 1.89 (95 % CI 1.43–2.51) and the dose–response effect was significant ($p = 0.0001$).

Meta-analyses

Three meta-analyses have been published recently. Asbridge et al. (2012) selected nine studies and concluded that driving under the influence of cannabis was associated with a significantly increased risk of motor vehicle collisions compared with unimpaired driving (OR 1.91; 95 % CI 1.35–2.73). They noted heterogeneity among the individual study effects, with higher collision risk estimates in case–control studies (2.79; 95 % CI 1.23–6.33) and studies of fatal collisions (2.10; 95 % CI 1.31–3.36) than in culpability studies (1.65; 95 % CI 1.11–2.46) and studies of non-fatal collisions (1.74; 95 % CI 0.88–3.46).

Li et al. (2012) included nine epidemiological studies in their meta-analysis and found an OR of 2.66 (2.07–3.41). Analysis of individual studies indicated that the heightened risk of crash involvement associated with marijuana use persisted after adjustment for confounding variables (including alcohol) and that the risk of crash involvement increased in a dose–response fashion with the concentration of THC-COOH detected in urine and the frequency of self-reported marijuana use. An analysis according to study design, type of drug assessment, study time period, study location and age of the subjects showed a more than twofold increased crash risk in each of the subsets of studies.

In another meta-analysis, Elvik (2013) found that the best estimate of the RR of accident involvement with cannabis, adjusted for publication bias, was 1.25 (95 % CI 0.87–1.79) for fatal accidents, 1.08 (95 % CI 0.86–1.36) for injury accidents and 1.14 (95 % CI 1.00–1.30) for crashes resulting in property damage.

Conclusion

The results of experimental studies clearly indicate that cannabis use can have a detrimental impact on driving ability, as it impairs some cognitive and psychomotor skills that are necessary for driving. Most of these effects increase in a dose-dependent way. A cannabis user is aware of the impairment, but can only partially compensate for it.

Acute effects: A study using fMRI found that, after use of cannabis, subjects were more attracted by intrapersonal stimuli ('self') and failed to attend to task performance, leading to insufficient allocation of task-orientated resources and suboptimal performance. Cannabis acutely reduces cognitive and psychomotor skills that are necessary for driving such as motor control, psychomotor speed, executive function, motor impulsivity, visual processing, short-term memory, working memory, perception and balance, and these effects are mostly dose dependent. In driving studies with low doses of cannabis, subjects were aware of the impairment and adjusted their driving style accordingly, but control deteriorated with increasing task complexity.

Duration of effects: The desired effect of cannabis, the 'high', lasts for up to 2 hours, but most studies found significant negative effects of cannabis on performance up to 10 hours after use.

Combinations: The risk of causing a crash by driving under the influence of alcohol and cannabis is similar to the product of the adjusted individual risks. Marijuana smokers tend to compensate effectively while driving by utilising a variety of behavioural strategies, but combining marijuana with alcohol eliminates the ability to use such strategies effectively.

Chronic use: Chronic use of cannabis can lead to deficiencies in memory, attention, manual dexterity, executive functioning and psychomotor speed. These effects can last longer than the period of intoxication and worsen with both increasing number of years and frequency of cannabis use. The defects are partially reversible with prolonged abstinence, but some impairment may be permanent. Very heavy use of marijuana is associated with persistent decrements in neurocognitive performance even after 3 or 4 weeks of abstinence.

Threshold concentration: Epidemiological studies showed that the risk of being in an accident is increased at THC concentrations above 1 or 2 ng/ml. Measurable THC concentrations after 7 days of abstinence indicate a potential mechanism for the residual neurocognitive impairment observed in chronic cannabis users.

Accident risk: Meta-analyses of data from epidemiological studies have shown that cannabis use is associated with a twofold increased risk of being involved in an accident. The risk of being involved in or responsible for a traffic accident is higher for the combination of alcohol and cannabis (OR approximately 15).

Opioids

Opioids can be divided into three groups, namely those with morphine-like activity (e.g. morphine, heroin, fentanyl and methadone), those that block the activity of morphine (e.g. naloxone and naltrexone) and those that exhibit mixed activity (e.g. codeine, buprenorphine and pentazocine) (Drummer, 2001). In this report, the acute and chronic effects and risks associated with the following opioids will be discussed: morphine, heroin, methadone, buprenorphine, fentanyl and codeine.

Fishbain et al. (2003) conducted a structured, evidence-based review of whether the driving-related skills of opioid-dependent or -tolerant patients are impaired. They found moderate, generally consistent, evidence of no impairment of psychomotor abilities and inconclusive evidence of no impairment of cognitive function. In addition, the evidence that there is no impairment of psychomotor abilities immediately after being given doses of opioids was strong and consistent. The evidence was also strong and consistent that the incidence of traffic violations or MVAs is not higher than in comparable control subjects. The analysis also revealed consistent evidence of no impairment of performance in driving simulators and off- or on-road studies. The authors also discuss possible causes for the inconsistent evidence in the cognitive impairment studies. One is the issue of unrelieved pain, as there is strong evidence that unrelieved pain may decrease psychomotor and cognitive performance. Another confounder could be educational level, as this has been shown to better correlate with measures of neuropsychological function than current or past levels of opioid use. In studies of cancer patients, disease state could be a confounder, as recent evidence indicates that, in cancer patients using opioids, the disease itself has the greatest impact on alertness. Another potential confounder in the studies in drug addicts is associated non-opioid drug abuse history; drug users with a history of alcohol dependence/abuse and/or polysubstance dependence/abuse show greater neuropsychological impairment than cocaine dependence/abuse addicts, who in turn will experience greater impairment than control subjects.

Acute effects

Morphine

Experimental studies have investigated the effects of single or repeated doses of morphine on healthy subjects in a laboratory setting. The results indicate that morphine can increase visual analogue scale ratings indicative of both pleasant (e.g. drug liking, increased calmness) and unpleasant (e.g. 'feel bad', 'nauseous') effects (Hill and Zacny, 2000; O'Neill et al., 2000; Walker et al., 2001). Hill and Zacny (2000) found that psychomotor impairment was absent after a single morphine dose of 5 or 10 mg/70 kg. Walker et al. (2001) compared the effects of cumulative morphine doses of 2.5, 7.5 and 17.5 mg/70 kg with the effects of mixed-action opioids. They found that morphine decreased performance on the DSST — in which speed decreased while accuracy was not affected — in a dose-dependent manner. Morphine also induced miosis and impaired eye–hand coordination in a dose-dependent manner. The impairment caused by morphine was of lower magnitude than that caused by mixed-action opioids. Knaggs et al. (2004) also observed an induction of miosis with morphine. Intravenous morphine (0.125 mg/kg) resulted in a 26 % decrease in pupil diameter in 10 healthy volunteers. O'Neill et al. (2000) administered repeated doses of morphine to subjects, and found one major effect, namely an increase in accuracy on the CRT task, but the speed of the response tended to be lower. Other effects were improvements in the accuracy of delayed recall and a reduction in the frequency at which fusion was detected in the CFF task. These effects lasted for up to 36 hours after repeated doses. The authors concluded that the effects of morphine were not substantial compared with those of lorazepam (one of the comparator drugs in the study).

In their meta-analysis of the experimental studies performed as part of the DRUID project, Strand et al. (2011) concluded that administration of a single dose of morphine of up to 5 mg appears to cause very few effects in traffic-relevant performance tasks. At higher doses, performance of various tasks is impaired, but with no clear dose–effect relationship except on the DSST. It is likely that blood morphine concentrations < 14 µg/l are accompanied by few effects in traffic-relevant performance tasks. Therefore, this level, 14 µg/l, could represent a level with little associated traffic risk.

An expert panel in Norway (Vindenes et al., 2012) proposed that, for the purpose of imposing sanctions, cut-off values for morphine in blood of 9, 24 and 61 µg/l should be considered equivalent to alcohol levels of 0.2, 0.5 and 1.2 g/l, respectively.

Fentanyl

Schneider et al. (1999) found that fentanyl in concentrations commonly used in outpatient surgical procedures (0.2 µg/kg) produces pronounced cognitive

impairment (auditory reaction time, signal detection, sustained attention, recognition) compared with placebo. Lichtor et al. (2002) investigated the effects on psychomotor function of ambulatory anaesthesia with propofol 2.5 mg/kg, propofol 2.0 mg/kg plus fentanyl 2 µg/kg, propofol 2.0 mg/kg plus midazolam 2 mg/70 kg or midazolam 0.07 mg/kg plus fentanyl 2 µg/kg. Psychomotor function was impaired up to 2 hours after injection with propofol alone and with each of the drug combinations. The multiple sleep latency test demonstrated sleepiness up to 8 hours after an injection of midazolam plus fentanyl. However, in driving simulator tests, Sinclair et al. (2003) found no significant impairment at 2, 3 or 4 hours after treatment with 2.5 mg/kg propofol plus 1 µg/kg fentanyl.

In their meta-analysis of the experimental studies performed as part of the DRUID project, Strand et al. (2011) concluded that fentanyl can be used acutely in procedures requiring pain relief at doses resulting in blood fentanyl concentrations up to 10 ng/ml before serious respiratory problems occur. Fentanyl has a half-life of 1–6 hours, which indicates that patients should refrain from driving for at least 12 hours after such dosages.

Heroin

No experimental studies on the acute effects of heroin in humans have been published since 1999. Therefore, a short overview will be given on the results of studies that were published before 1999. Several studies confirmed the acute effects of heroin on subjective sedation and on miosis (Cone et al., 1993; Jasinski and Preston, 1986; Jenkins et al., 1994; Martin and Fraser, 1961). One study found a trend towards decreased performance on the CLT, which is an indicator of psychomotor performance (Cone et al., 1993). In another study, the administration of heroin impaired performance on a reaction time task (Jenkins et al., 1994). However, the doses used in these studies ranged from 2 to 20 mg, while average daily doses in addicts range from 300 to 500 mg (Couper and Logan, 2004a). The effects of heroin on performance can last up to 6 hours (Cone et al., 1993; Jasinski and Preston, 1986; Jenkins et al., 1994; Martin and Fraser, 1961). The duration of the effects is dependent upon the dose and the route of administration. For example, Jenkins et al. (1994) assessed subjective effects of sedation, miosis and increased reaction time that lasted for 2 hours after smoking and 4 hours after intravenous administration.

Pharmacology of heroin

Heroin is a crude preparation of diamorphine. It is a semisynthetic product obtained by acetylation of morphine, which occurs as a natural product in opium: the dried latex of certain poppy species (e.g. *Papaver somniferum* L.).

Diamorphine, like morphine and many other opioids, produces analgesia. It behaves as an agonist at a complex group of receptors (the µ, κ and δ subtypes) that are normally acted upon by endogenous peptides known as endorphins. Apart from analgesia, diamorphine produces drowsiness, euphoria and a sense of detachment. Negative effects include respiratory depression, nausea and vomiting, decreased motility in the gastrointestinal tract, suppression of the cough reflex and hypothermia. Tolerance and physical dependence occur with repeated use. Cessation of use in tolerant subjects leads to characteristic withdrawal symptoms. Subjective effects following injection are known as 'the rush' and are associated with feelings of warmth and pleasure, followed by a longer period of sedation. Diamorphine is two to three times more potent than morphine. The estimated minimum lethal dose is 200 mg, but addicts may be able to tolerate 10 times as much. Following injection, diamorphine crosses the blood–brain barrier within 20 seconds, with almost 70 % of the dose reaching the brain. It is difficult to detect in blood because of rapid hydrolysis to 6-monoacetylmorphine and slower conversion to morphine, the main active metabolite. The plasma half-life of diamorphine is about 3 minutes.

Source: EMCDDA drug profiles (http://www.emcdda.europa.eu/publications/drug-profiles).

Methadone

Several studies have investigated the effects on performance of substances used for substitution treatment. In a study of the acute effects of methadone in patients admitted to an opioid detoxification programme, patients were tested after 3 and 5 days of methadone treatment (Curran et al., 2001). Performance on an episodic memory task was significantly impaired following the 100 % daily dose of methadone. The effect could, however, be avoided by giving methadone in

divided doses. No effects were observed on DSST, FTT and digit cancellation records.

In their meta-analysis performed as part of the DRUID project, Strand et al. (2011) found that single doses of methadone of up to 10 mg impaired performance on three out of five tests administered to drug-naive, healthy subjects. When single doses of methadone were administered to opioid users, these acute effects were less pronounced. When single doses of methadone were administered to methadone-maintained patients, the acute effects of methadone also appeared to be less pronounced, as dose-related impairment of performance on 10 out of 50 tests was found following administration of methadone doses of up to 120 mg. Regarding performance of methadone maintenance patients compared with control subjects, 110 out of 236 tests showed impairment. Four studies have compared the performance before and after long-term methadone intake; one of the studies found impairment and one found improvement from baseline measures.

An expert panel in Norway (Vindenes et al., 2012) proposed that, for the purpose of imposing sanctions, a cut-off value for methadone in blood of 25 ng/ml should be considered equivalent to an alcohol concentration of 0.2 g/l.

Buprenorphine

As a partial opioid receptor agonist, buprenorphine has a ceiling effect on its agonist activity, which greatly increases its safety profile relative to full-agonist medications such as methadone. Strain et al. (2000) administered sublingual buprenorphine (4, 8 or 16 mg) or a combination of sublingual buprenorphine and naloxone to seven non-dependent opioid users, and investigated the effects on psychomotor and cognitive performance. Results on the DSST showed no significant changes at any of the dose conditions tested, and there were no significant differences in the total number of sequence errors made on a TMT. However, the highest buprenorphine/naloxone dose (16/4 mg) produced a significantly higher total line length for the trails. The CLT showed significant decreases in performance with 16 mg buprenorphine. The same researchers investigated the effects of a single intramuscular or sublingual administration of combined buprenorphine and naloxone at various doses in opioid-dependent subjects. There was no evidence that sublingual buprenorphine and naloxone impairs psychomotor performance. There were no significant effects of any test condition on the trails' total length or total errors or on the DSST's number attempted, number correct or percentage errors. CLT performance was decreased at the highest intramuscular dose (16/4 mg). There was also a significant increase in the number of trails' sequence errors for the two highest intramuscular doses of buprenorphine/naloxone (Stoller et al., 2001). Comer et al. (2002) studied the effects of intravenously administered buprenorphine (2 or 8 mg) or placebo on the performance of detoxified heroin users on a DSST, a divided attention task, a rapid information processing task and a repeated acquisition of response sequences task. There were few effects of buprenorphine on performance, with the exception of impairments in performance on the divided attention task. The latency to respond to a brief target randomly appearing on the computer screen was greater, the number of missed targets significantly increased and the number of correctly identified targets significantly decreased. Dagtekin et al. (2007), in a prospective trial, compared 30 patients suffering from chronic non-cancer pain who had been treated with stable doses of transdermal buprenorphine with 90 healthy volunteers (matched pairs). Driving ability, defined as a result above the 16th percentile for normal subjects (individuals performing worse than the 16th percentile of the control group are considered to be unable to drive according to German law), did not differ significantly between the patients and the control group. The authors concluded that long-term use of transdermal buprenorphine for chronic non-cancer pain does not impair driving ability, but, because of the individual variability of test results, an individual assessment is recommended.

Shmygalev et al. (2011), using a battery of tests, performed a prospective comparison of opioid substitution patients receiving sublingual buprenorphine and a control group of untreated, healthy volunteers. Patients receiving a stable dose of sublingual buprenorphine showed no significant impairment of complex psychomotor or cognitive performance compared with healthy control subjects. However, intake of illicit drugs as well as the lack of social reliability were major problems in this specific patient group. The authors concluded that, despite the absence of a relevant impact of the drug on driving ability, such patients should not be allowed to hold a driving licence.

In their meta-analysis performed as part of the DRUID project, Strand et al. (2011) found that single-dose buprenorphine (0.075–0.6 mg/kg intravenous, 0.4 mg oral, 0.3 mg intramuscular) impaired performance in 18 out of 20 tests administered to drug-naive healthy volunteers. When single doses were administered to opioid users, these acute effects were less pronounced. In patients maintained on methadone or buprenorphine, doses of up to 13.4 mg buprenorphine resulted in

impairment in only 2 out of 21 tests. Furthermore, in 3 out of 21 tests carried out in methadone- or buprenorphine-maintained patients, performance improved after buprenorphine doses of 4 to 13.4 mg. Buprenorphine-maintained patients showed impairment, relative to control subjects, on 14 out of 44 tests.

An expert panel in Norway (Vindenes et al., 2012) proposed that, for the purposes of sanctions, a cut-off value for buprenorphine in blood of 0.9 ng/ml should be considered equivalent to an alcohol concentration of 0.2 g/l.

Codeine

Bachs et al. (2009) performed a prospective cohort trial using data from national population-based registries — the Norwegian Prescription Database and the Norwegian Road Accident Registry — and observations of over 8 million person-years were used in order to examine whether a driver who has filled a prescription for codeine or tramadol is at increased risk of being involved in a road accident resulting in injury to persons. The risk of being involved in an accident was significant for drivers using codeine [standardised incidence ratio (SIR) for both sexes and all age groups combined: 1.9; 95 % CI 1.6–2.2]. The SIR for tramadol (1.5; 95 % CI 0.9–2.3) was not significant but showed an upward trend. Nilsen et al. (2011) performed a driving simulator study in 20 patients with chronic pain on long-term codeine therapy, 20 chronic pain patients not using codeine and 20 healthy control subjects. The patients using codeine 120–270 mg (mean 180 mg) daily showed the same driving skills as patients not using codeine, and the codeine level did not affect the results, either 1 hour after intake of a single dose of 60 mg codeine or ≥ 5 hours after the last codeine intake. Reaction times in both rural and urban driving conditions were significantly higher in the patients with chronic pain than in the healthy control subjects (difference 0.11 seconds and 0.12 seconds, respectively). The chronic pain patients missed almost twice as many reactions to traffic signs. There was no difference between the groups in steering precision. Codeine did not impair driving-related abilities over and above what is associated with chronic pain per se.

In the meta-analysis performed as part of the DRUID project (Strand et al., 2011), the lowest impairing dose of codeine was 25 mg. The half-life of codeine is 2–4 hours. Thus, 4 hours after an intake of 50 mg there could still be impairing effects comparable to the acute effects after an intake of 25 mg codeine. A therapeutic schedule with dosing of 50 mg every 6 hours would probably be unsafe in the sense that it could cause impairment in some traffic-relevant tasks.

One of the DRUID project's experimental studies (Schulze et al., 2012) concluded that combinations of codeine and paracetamol in general did not produce driving impairment when administered to healthy volunteers even at higher doses. However, driving impairment became apparent after the lowest dose when paracetamol was administered to elderly subjects. Thus, the results indicate that the impairing potential of codeine and paracetamol varies with age.

Dose change

Gaertner et al. (2008) conducted a prospective trial in patients suffering from chronic non-cancer pain in order to examine the effects of the daily dose of opioids on psychomotor and cognitive functions. A computerised test system was administered to patients before and 7 days after alteration of their opioid therapy. Seven days after an increase in the daily dose of an opioid or after the initiation of opioid therapy there was no general deterioration in patients' driving ability at group level.

Gomes et al. (2013) conducted a population-based nested case–control study of patients aged 18–64 years who received at least one publicly funded prescription for an opioid and demonstrated that, compared with very low opioid doses, drivers who were prescribed low doses had a 21 % increased odds of road trauma (adjusted OR 1.21; 95 % CI 1.02–1.42); those prescribed moderate doses had a 29 % increased odds (adjusted OR 1.29; 95 % CI 1.06–1.57); those prescribed high doses had a 42 % increased odds (adjusted OR 1.42; 95 % CI 1.15–1.76); and those prescribed very high doses had a 23 % increased odds (adjusted OR 1.23; 95 % CI 1.02–1.49).

Chronic effects

Opioid therapy

Larsen et al. (1999) compared attention and reaction time in patients on long-term opioid therapy (patients with cancer pain or chronic non-malignant pain), patients receiving non-opioid analgesic therapy for chronic non-malignant pain and a control group of patients without pain or analgesic therapy. No significant difference in attention/concentration between the three groups could be demonstrated. However, attention/concentration was more impaired in cancer patients

than in non-cancer patients taking opioids. Auditory and optical reaction times were significantly higher in patients on opioids than in the non-opioid analgesic group and very significantly higher than in the control group. Galski et al. (2000) determined the effects of medically prescribed stable opioid use on the driving abilities of patients with persistent, non-malignant pain, using a pre-driver evaluation, a simulator evaluation and behavioural observation during simulator performance. The control group consisted of cerebrally compromised patients who had undergone the same evaluation. The opioid-treated patients generally outperformed the control group. However, the opioid-treated patients had significant difficulty in following instructions and their ratings were more similar to the subjects in the control group who had failed than to the ratings of those who passed the evaluation. Sjogren et al. (2000a) assessed neuropsychological performance in chronic non-malignant pain patients receiving long-term oral opioid therapy and in a control group of healthy volunteers. The neuropsychological tests consisted of continuous reaction time, FTT and PASAT. The patients performed more poorly than the control subjects in all the tests, with the differences being statistically significant. Significantly positive correlations were found between the results on the PASAT and the pain visual analogue scales. The authors concluded that pain itself seems to have an arousal effect on working memory. The same research group evaluated the effects of oral opioids and pain on performance of cancer patients on the same neuropsychological tests (Sjogren et al., 2000b). The use of long-term oral opioid treatment per se did not affect neuropsychological performance and, according to the authors, pain itself, more than oral opioid treatment, worsens performance on PASAT. Strumpf et al. (2005) studied the safety-relevant performance of patients receiving chronic opioid therapy. The patients' results were worse on a concentration test and better on a coordination test than the results of healthy control subjects. The patients did not perform worse than healthy control subjects on tests of reaction time, vigilance and perception. Patients receiving an antidepressant in addition to the opioid performed more poorly on the test for concentration than patients not on antidepressants. Pain intensity did not influence patients' results, nor did opioid dose, state of mind or side-effects. Byas-Smith et al. (2005) compared the psychomotor performance and driving ability of patients with chronic pain managed with stable opioid doses with that of healthy control subjects. Patients were evaluated for errors while driving their own car along a predetermined route in the community, including variable residential and highway conditions, and for speed and accuracy on repeated trials through a five-station obstacle course that evaluated forward and reverse driving, turning and parallel parking. No significant differences were observed between the group of patients and the control group.

Several experimental studies have investigated the effects of chronic use of specific opioids. Raja et al. (2002) compared the cognitive and psychomotor effects of morphine versus a TCA in patients with neuropathic pain syndrome. Each subject received approximately 8 weeks each of morphine, nortriptyline and placebo. Patients who could not tolerate a drug were offered an alternative drug of the same class within that period; for morphine, the alternative was methadone. Performance was measured on the symbol substitution task from the WAIS (concentration and psychomotor function), the Hopkins verbal learning test and the grooved pegboard task (manual dexterity and psychomotor speed). Treatment with opioids did not influence performance on any measure. Tassain et al. (2003) investigated the long-term effects of oral sustained-release morphine on neuropsychological performance in patients with chronic non-cancer pain. Evaluations were performed at baseline in patients free from opioids and then after 3, 6 and 12 months. There was no impairment of any neuropsychological variable over time in the morphine-treated patients compared with the control group. Information processing speed was improved at 6 and 12 months and there were significant correlations with pain relief and improvement of mood. Patients, however, often require more pain relief than is afforded by sustained-release opioid drugs. Kamboj et al. (2005) examined the effects of additional immediate-release doses of morphine on cognitive functioning in patients receiving chronic opioid therapy in palliative care. The results suggested that immediate-release morphine, when taken on top of a sustained-release opioid, produces transient anterograde and retrograde memory impairments and a decrement in two-target tracking.

In pre-marketing clinical trials of transdermal fentanyl, somnolence and confusion each occurred in more than 10 % of the 153 cancer patients, and tremor, abnormal coordination, abnormal gait, amnesia and syncope each occurred in 1 to 2 % (Kornick et al., 2003). Sabatowski et al. (2003) compared the performance of patients with continuous non-cancer pain, who had received stable doses of transdermal fentanyl for at least 2 weeks, on a series of computerised tests to measure attention, reaction, visual orientation, motor coordination and vigilance with the performance of healthy control subjects. None of the performance measures was significantly inferior in the group of patients compared with the control group. In a study of the psychomotor effects of long-term fentanyl use, patients with low back

pain were administered two neuropsychological tests (DSST and TMT) before being prescribed opioids for pain, and tests were readministered after 90 and 180 days (Jamison et al., 2003). No impaired cognition or psychomotor function was observed, and, in fact, test scores were even significantly improved while subjects were taking opioids for pain. Menefee et al. (2004) compared the baseline performance of patients taking oxycodone with their performance after being stabilised for 1 month on transdermal fentanyl. The tests included driving performance in a driving simulator as well as cognitive and balance tests. No differences were found in driving simulation measures between the pre- and post-treatment periods. No decrements in cognitive performance were found, nor were there differences in balance or body sway. Improvements in visual motor tracking, visual memory and attention were observed during treatment with transdermal fentanyl.

The fact that pain plays a role in the cognitive defects detected in pain patients was confirmed in a study by Veldhuijzen et al. (2006a), who determined the effects of chronic non-malignant pain on actual highway driving performance during normal traffic. In addition, driving-related skills (tracking, divided attention and memory) were examined in the laboratory. Subjective driving quality was rated on visual analogue scales. The results showed that a subset of pain patients had SDLP values that were higher than those of the matched healthy control subjects, which resulted in an overall statistically significant difference in SDLP between pain patients and healthy controls. Further, chronic non-malignant pain patients rated their subjective driving quality to be normal, although their ratings were significantly lower than those of the healthy control subjects. No significant effects were found in the laboratory tests.

In one of the DRUID project's experimental studies (Schulze et al., 2012), the results of the driving tests revealed that the driving performance of patients suffering from chronic pain and receiving long-term treatment with opioid analgesics was similar to that of healthy control subjects. Nevertheless, neuropsychological tests assessing skills related to driving revealed that pain patients performed worse than healthy controls on a number of tests.

In their meta-analysis performed as part of the DRUID project, Strand et al. (2011) concluded that the literature is too limited to draw clear conclusions regarding the effects of long-term medical use of morphine and driving. It is, however, possible that drug effects of relevance to driving are not marked in such patients. Therefore, evaluation of individual performance of such patients seems, with the present knowledge, to be the only useful procedure to approach the question of fitness for driving.

Meta-analyses

Mailis-Gagnon et al. (2012) included 35 studies (2 044 patients, 1 994 control subjects) in a systematic review of the quality and generalisability of studies on the effects of opioids on driving and cognitive/psychomotor performance. Of the included studies, 9 %, 54 % and 37 % were of poor, fair and high quality, respectively; three-quarters of the studies used high-sensitivity cognitive tests. Dose of opioids varied largely in many studies. The mean number of possible but unreported confounders was 2.2 (range 0–4), and related mainly to the failure of the studies to mention co-prescriptions with psychotropic effects, pain severity, sleep disorder or daytime somnolence and/or significant depressive or anxiety-related problems. The authors concluded that the commonly held concept that chronic pain patients on stable opioids can safely drive cannot be generalised to all such patients in everyday practice, but may be applicable to only a subset who meet certain criteria.

Dassanayake et al. (2011) performed a meta-analysis of epidemiological and experimental evidence and found that limited epidemiological research reported that opioids may be associated with increased accident risk in the first few weeks of treatment.

Heroin dependence

Chronic heroin use can have long-lasting effects on some cognitive and psychomotor skills. Studies have found an impairment of planning function (Bryun et al., 2001), reaction time (Liu et al., 2006), time perception (Alexandrov, 2004), spatial working memory (Ornstein et al., 2000), pattern recognition memory (Ornstein et al., 2000), executive functioning (Lyvers and Yakimoff, 2003; Ornstein et al., 2000; Verdejo et al., 2004) and right–left discrimination (Ning et al., 2005). Chronic heroin users also tend to be reckless and ignore the rules and regulations of tasks (Pau et al., 2002). For some tasks, there is a significant relationship between the severity of heroin dependence or duration of use and the level of impairment (Bryun et al., 2001; Lyvers and Yakimoff, 2003; Verdejo et al., 2004). For example, male addicts with a duration of use longer than 1.5 years perform worse on a Tower of London task than addicts with a shorter duration of use (Bryun et al., 2001). Some chronic effects can persist for more than a year after the last use of the drug (Pau et al., 2002), whereas some impairments last only a short period; for example, the

effect on time perception disappears after 15 days of abstinence (Alexandrov, 2004).

Substitution treatment (methadone and buprenorphine)

The effects of substitution treatment on performance have been studied in former heroin addicts. Dittert et al. (1999) compared the performance of 28 patients taking methadone on reaction, visual perception and concentration tests with that of a control group matched for age, sex and education level. The methadone-treated patients showed significantly reduced performance, but six of them passed the tests to a level corresponding to sufficient driving skills. Darke et al. (2000) found that patients receiving methadone maintenance treatment showed cognitive deficits compared with a control group not using heroin. The patients' performance was significantly worse than that of controls on all neuropsychological domains measured: information processing, attention, short-term visual memory, delayed visual memory, short-term verbal memory, long-term verbal memory and problem-solving. A history of alcohol dependence and repeated exposure to overdose increased the likelihood of cognitive impairment. The authors remarked that it was possible that other factors (which they did not specify) that were not measured in the study may have contributed to the cognitive impairment. In another study of methadone-maintained patients, higher speed in decision-making and motor reaction, but more decision errors on a simple CRT, were observed in patients than in healthy control subjects (Specka et al., 2000). The patients also showed poorer performance on an attention task and a tachistoscopic perception task. Performing a tracking test and a test concerning visual structuring, patients showed a higher accuracy combined with more time needed. However, the effects were moderate and, in most cases, the observed variance could be better explained by sociodemographic features than by treatment group. The authors suggest the need to investigate whether impairments in one area of demand are not compensated by, for example, reducing speed. Mintzer and Stitzer (2002) found that patients on methadone maintenance treatment exhibit impairment relative to healthy control subjects in psychomotor speed, working memory, decision-making and metamemory. The results also suggested possible impairment in inhibitory mechanisms. There was no impairment observed in time estimation, conceptual flexibility or long-term memory. The control group used in these three studies (Darke et al., 2000; Mintzer and Stitzer, 2002; Specka et al., 2000) consisted of subjects who were not addicted to heroin. The observed effects in the patients on methadone could thus be caused partially by the heroin addiction rather than the methadone treatment.

Some experimental studies have tried to differentiate between impairment caused by heroin addiction and impairment caused by methadone treatment. Davis et al. (2002) compared neuropsychological performance in methadone-maintained patients with that of drug-free ex-opioid users and of matched control subjects with no history of drug abuse. Methadone-maintained patients performed more poorly on a measure of verbal fluency than the two control groups. The performance of the drug-free ex-opioid users fell between that of the other two groups, without significant differences. Verdejo et al. (2005) also compared patients on methadone maintenance treatment with abstinent heroin users in terms of neuropsychological performance. A significantly slower performance was seen in methadone patients on processing speed, visuospatial attention and cognitive flexibility tests, and less accuracy was observed on working memory and analogical reasoning tests. Mintzer et al. (2005) also observed that the cognitive and psychomotor performance of patients on methadone maintenance treatment was worse than that of abstinent former opioid users, whose performance was in turn worse than that of healthy control subjects. These data suggest that methadone maintenance may be associated with additional impairment over and above that associated with long-term heroin abuse. Gruber et al. (2006) compared cognitive function in 17 opioid-dependent subjects at baseline and after 2 months of methadone treatment. Significant improvements from baseline were seen in measures of verbal learning and memory, visuospatial memory and psychomotor speed. These improvements remained significant after co-varying for illicit drug use. The authors suggest that impairment caused by methadone maintenance treatment may be reversible.

In a randomised controlled trial comparing the effects of a 28-day withdrawal treatment with either buprenorphine or clonidine on DSST performance in opioid-dependent adolescents, no evidence of psychomotor impairment was observed (Marsch et al., 2005). Mintzer et al. (2004) evaluated the dose-related effects of buprenorphine/naloxone combination therapy in opioid-dependent volunteers following a period of 7–10 days of administration, in a double-blind, within-subject, crossover design. The tests included measures of psychomotor speed, time perception, conceptual flexibility, focused attention, working memory, long-term/episodic memory and meta-memory. The results revealed little impairment in performance as the dose was increased fourfold (from 8/2 mg to 32/8 mg). The only significant effect of dose was impairment of

episodic/long-term memory at the highest dose, relative to the two lower doses.

Rogers et al. (1999) assessed decision-making in 13 opioid users, three of whom were using heroin and 10 of whom were receiving methadone. Compared with healthy volunteers, the opioid users were found to deliberate for a significantly longer time before making their choices. There was, however, no difference in the quality of decision-making.

Comparison of chronic effects of the two main substitution treatments

Soyka et al. (2001) found an overall better psychomotor performance in patients taking buprenorphine than in those taking methadone, especially in tests under stress conditions and monotony. These findings were confirmed by several other studies. Schindler et al. (2004) found that opioid-dependent patients receiving maintenance treatment with either methadone or buprenorphine performed worse than control subjects on an attention test under monotonous circumstances and on decision and reaction time while driving in a dynamic environment. However, when separated into treatment groups, the mean decision and reaction times of buprenorphine-maintained patients did not differ from those in the control group, whereas patients on methadone showed significantly prolonged mean decision and reaction times. A controlled clinical study also showed that buprenorphine produces less impairment of cognitive functions on psychomotor testing than methadone (Soyka et al., 2005). Pirastu et al. (2006) evaluated decision-making in individuals on maintenance treatment with methadone or buprenorphine and in a control group of subjects who were not drug dependent. Subjects on buprenorphine performed better on the Iowa gambling task than those taking methadone, and about the same as the control group. The methadone group made more perseverative errors on the WCST than the control group, whereas the buprenorphine group had intermediate scores. Scores on the WAIS-revised and the BVRT were similar for both opioid-dependent groups, whereas the drug-free control group had significantly higher scores. The effects of methadone and buprenorphine substitution treatment on performance in a driving simulator were studied by Lenné et al. (2003). All participants attended one session without alcohol and one session with alcohol (BAC of 0.5 g/l). SDLP, speed and steering wheel angle were used to measure simulated driving skills, and reaction time to a subsidiary task was also assessed. While the combination with alcohol impaired all measures of driving performance, there were no differences in driving skills across the participant groups. Giacomuzzi et al. (2005a) compared the driving capacity of drug-dependent patients using buprenorphine or slow-release oral morphine. The data indicated better psychomotor performance in patients taking buprenorphine, especially on the visual pursuit test. The same researchers compared the driving capacity of patients treated with methadone or slow-release oral morphine, and observed better psychomotor performance in patients taking methadone (Giacomuzzi et al., 2005b).

McNamara (2002) studied cognitive function and well-being in patients switching treatment from morphine to transdermal fentanyl. Cognitive function tests revealed a significant improvement in working (short-term) memory and speed of memory although not in secondary (long-term) memory. The incidence of dizziness was significantly reduced, and sleepiness and drowsiness were significantly less of a problem.

Baewert et al. (2007) evaluated driving aptitude (in a simulator) and traffic-relevant performance (on relevant tests) at peak and trough medication levels in 40 opioid-dependent patients receiving maintenance therapy with either buprenorphine (mean dose 13.4 mg) or methadone (mean dose 52.7 mg). Traffic-relevant performance was analysed 1.5 hours (peak level) and 20 hours (trough level) after administration of opioid maintenance therapy. The results showed that patients had significantly more incorrect reactions ($p = 0.03$) and made significantly more simple errors ($p = 0.02$) when the level of medication was lowest than when drug levels were at their peak. In addition, the study found that, when drug levels were at their peak, methadone-maintained patients tended to perform less well than buprenorphine-maintained patients on some of the test items. This investigation indicated that opioid-maintained patients did not differ significantly at peak versus trough level in the majority of the investigated items and that neither substance appears to affect traffic-relevant performance when given as maintenance therapy in a population in whom concomitant consumption can be excluded.

In their meta-analysis performed as part of the DRUID project, Strand et al. (2011) found that eight studies compared the performance of buprenorphine-maintained patients with that of methadone-maintained patients. Overall, patients receiving buprenorphine performed better than those receiving methadone in 10 out of 59 tests. The differences between buprenorphine-maintained patients and matched control subjects seemed less evident than for methadone.

Risks

Accident risk

In a longitudinal study of 13 548 participants from a cohort study of workers in France from 1989 to 2000, the risk of a serious accident was compared among participants who did and did not report a specific health problem during the 12 months before the accident (Lagarde et al., 2005). The results indicated that pain and treatment for pain could increase the risk of a road traffic accident.

Epidemiological studies have investigated the risk of being involved in a traffic accident while driving under the influence of opioids. A case–control study in Canada showed that driving under the influence of opioids is not associated with an increased accident risk (RR 2.1; 95 % CI 0.8–5.3) (Dussault et al., 2002). In contrast, a case–control study in France found that morphine use is associated with an increased accident risk (OR 8.2; 95 % CI 2.5–27.3) (Laumon et al., 2005). In the Netherlands, the Immortal study, which performed different case–control studies between 2002 and 2005, found that use of codeine alone is not associated with an increased accident risk (RR 3.0; 95 % CI 0.7–14.2), whereas use of heroin or morphine alone is associated with an increased accident risk of 32.4 (OR; 95 % CI 1.8–592.0) (Assum et al., 2005). The results of the Immortal study in Norway also showed that driving under the influence of any opioid alone (morphine, heroin or codeine) is associated with an increased accident risk of 13.8 (OR; 95 % CI 1.2–154.2) (Assum et al., 2005).

In a registry-based cohort study, Engeland et al. (2007) compared the incidence of accidents, as measured by the SIR, in the exposed person-time with the incidence in the unexposed person-time. The risk was markedly increased in users of natural opium alkaloids (SIR 2.0; 95 % CI 1.7–2.4). Somewhat increased SIRs were found for non-steroidal anti-inflammatory drugs (1.5; 95 % CI 1.3–1.9).

Bernard et al. (2009) studied 635 drivers suspected of driving under the influence of drugs in Norway between 2000 and 2006 in whom methadone was subsequently detected in a blood sample. They found that confirmed cases of driving impairment involving methadone alone were very rare, with combination use more frequent. No correlation between blood methadone concentration and impairment, as judged by the clinical test for impairment, was seen in either clinically impaired drivers or for the drivers as a whole.

In a cohort study performed in Norway, Bramness et al. (2012) linked data from three administrative registries (Norwegian Prescription Database on any prescriptions ever received by the individuals for methadone and benzodiazepines, Norwegian Road Accident Registry with information about MVAs involving personal injuries and Central Population Registry with demographic information on all residents in Norway) using unique person identifiers. During the 4 626 person-years of exposure to methadone, there were 26 MVAs. There were very few accidents among females who received methadone and women showed no increased risk of being involved in MVAs (SIR 1.1; 95 % CI 0.2–3.1). The authors observed an increased risk of involvement in accidents among males (SIR 2.4; 95 % CI 1.5–3.6).

Meuleners et al. (2011), in a retrospective, population-based, case-crossover study in Western Australia, examined the association between psychoactive medications and crash risk in drivers aged 60 and older. The risk of a crash necessitating hospitalisation was higher in drivers who were taking prescribed opioid analgesics (OR 1.5; 95 % CI 1.0–2.3). Women who were prescribed opioid analgesics (OR 1.8; 95 % CI 1.1–3.0; $p = 0.03$) had a significantly greater crash risk, but men did not.

Based on the DRUID results in Belgium, Kuypers et al. (2012) calculated an adjusted OR for a crash resulting in injury of 2.91 (95 % CI 0.97–8.68) for medicinal opioids. For illicit opioids, only the crude OR could be calculated: 4.57 (95 % CI 0.47–44.15).

In the DRUID case–control study (Hels et al., 2011), based on data for all countries, the relative risk of serious injury when driving while under the influence of medicinal opioids was estimated to be moderately increased (RR 2–10). The adjusted OR was 9.06 (95 % CI 6.40–12.83) for serious injury and 4.82 (95 % CI 2.60–8.93) for death. For illicit opioids, the risk was also estimated to be moderately increased (95 % CI 2–10). The adjusted OR, based on data for all countries, was 2.47 (95 % CI 0.50–12.10) for serious injury. For the risk of death, only a crude OR could be calculated: 10.04 (95 % CI 2.04–49.32).

Responsibility analyses

Three epidemiological studies have studied the risk of being responsible for a traffic accident while driving under the influence of opioids. Drummer et al. (2004) found that driving under the influence of opioids alone is not associated with an increased risk of responsibility for an accident (OR 1.4; 95 % CI 0.7–2.9). According to the

authors, however, this does not mean that opioid use does not increase the risk of a driver being responsible for a crash. Because 65 % of the opioid-positive drivers in the study who were also using other drugs (predominantly benzodiazepines and cannabis) were excluded from the analysis, the statistical power of the analysis was greatly reduced. In addition, some drivers would have been tolerant to the effects of opioids and effectively misclassified as opioid-intoxicated, further reducing the study's ability to detect a real association between opioids and accident responsibility. Dussault et al. (2002) found that driving under the influence of opioids is associated with an infinite risk of responsibility for an accident. This is probably because all of the small number of fatally injured drivers testing positive for opioids were judged to have been responsible for the accident. In a study by Laumon et al. (2005), a blood concentration of opioids above 20 ng/ml was not associated with an increased risk of responsibility for a fatal accident (OR 0.9; 95 % CI 0.6–1.5); however, the OR was not adjusted for confounding factors.

Corsenac et al. (2012) extracted and matched data from three French national databases — the national healthcare insurance database, police reports and the national police database of injurious crashes — and performed a case–control analysis comparing responsible versus non-responsible drivers. Injured drivers exposed to buprenorphine or methadone on the day of the crash had an increased risk of responsibility for the crash (OR 2.02; 95 % CI 1.40–2.91). The increased risk could be explained by the combined effect of risky behaviours and treatments. A French registry-based study on the risk of road traffic crashes in people who were prescribed medicines (Orriols et al., 2010) found an OR of 1.04 (95 % CI 0.94–1.15) for analgesics [class N02 in the Anatomical Therapeutic Chemical (ATC) classification; this class includes opioids, other analgesics and antipyretics and antimigraine preparations].

Meta-analyses

In their meta-analysis of 21 epidemiological studies (13 case–control and eight cohort studies), Dassanayake et al. (2011) found that limited epidemiological research reported that opioids may be associated with increased accident risk in the first few weeks of treatment.

In his systematic review and meta-analysis, Elvik's (2013) best estimate of the relative risk of opioid users being involved in an accident resulting in death, injury or property damage, adjusted for publication bias, was 1.44 (95 % CI 0.86–2.40), 1.89 (95 % CI 1.47–2.43) and 4.76 (95 % CI 2.10–10.80), respectively.

Conclusion

Acute effects: Opioids acutely cause some cognitive and psychomotor impairment, but these effects are highly dependent on the type of opioid and the dose administered. The effects are mostly moderate. Single-dose administration of morphine in doses up to 5 mg appears to cause very few effects in traffic-relevant performance tasks. At higher doses impairment is found in various tasks, but with no clear dose–effect relationship. Fentanyl in doses commonly used in outpatient surgical procedures produces pronounced cognitive impairment, but no significant impairment remains at 2, 3 or 4 hours after treatment. Single doses of methadone appear to be followed by impairment in drug-naive subjects, but these acute effects are less pronounced in opioid users. Acute effects of methadone can be avoided by dividing the daily dose. Long-term use of transdermal buprenorphine for the treatment of chronic non-cancer pain does not impair driving ability, but, because of the individual variability of test results, an individual assessment is recommended. Drivers using codeine have an increased risk of being involved in an accident, but codeine does not impair driving-related abilities over and above what is associated with chronic pain per se.

Duration of effects: Psychomotor function is impaired up to 2 hours after administration of fentanyl. The effects of heroin on performance can last up to 6 hours. Codeine has impairing effects 4 hours after an intake of 50 mg.

Chronic use: Heroin users show clear impairment of psychomotor and cognitive skills, some of which can last for more than a year after the last use of the drug. Patients on long-term opioid therapy exhibit some impairment of psychomotor and cognitive performance. However, the effect of the opioid drug itself on impairment in patients receiving opioid maintenance therapy is unclear. Other factors, such as the disease and pain, seem to be of greater importance than the effects of the opioids per se. The concept that chronic pain patients on stable opioids can drive safely cannot be generalised to all such patients in everyday practice, but may be applicable to only a subset that meet certain criteria. Evaluation of individual performance of such patients seems, with the present knowledge, to be the only useful procedure to approach the question of fitness for driving. There is increased accident risk in the first few weeks of treatment. Methadone maintenance treatment does cause impairment, including additional impairment over and above that associated with heroin

dependence, though the latter can in some cases be better explained by other associated risk factors. Impairment caused by methadone maintenance treatment may be reversible. Buprenorphine users have not generally shown impairment, except at high doses.

Threshold concentration: An expert panel in Norway proposed cut-off blood values of 0.9 ng/ml for buprenorphine, 25 ng/ml for methadone and 9 ng/ml for morphine, each corresponding to an alcohol concentration of 0.2 g/l. For morphine the limit was 24 ng/ml, equivalent to a BAC of 0.5 g/l.

Accident risk: The limited epidemiological studies available provide inconclusive evidence for the accident risk associated with opioid use. Some studies found significantly elevated accident risks associated with driving under the influence of opioids. Three out of five responsibility analyses found no increased risk of responsibility for an accident while under the influence of opioids. A systematic review found that limited epidemiological research reported that opioids may be associated with increased accident risk in the first few weeks of treatment. Injured drivers exposed to buprenorphine or methadone on the day of the crash had an increased risk of responsibility for the crash (OR 2.02). In a meta-analysis the relative risk of opioid users being involved in an accident involvement resulting in death, injury or property damage accidents was 1.44 (95 % CI 0.86–2.40), 1.89 (95 % CI 1.47–2.43) and 4.76 (95 % CI 2.10–10.80), respectively.

Amphetamines

On the illicit drug market, the main representatives of the amphetamines group are amphetamine, methamphetamine and their salts. MDMA is also a derivative of amphetamine and a member of the phenethylamine family (as are amphetamine and methamphetamine).

It is important to mention that the doses of amphetamine and methamphetamine administered in the experimental studies described below were very low (10–30 mg), and thus not representative of realistic situations (100–1 000 mg/day) (Couper and Logan, 2004a).

No recent experimental studies were found for the designer amphetamines 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethylamphetamine (MDEA) and *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB).

Pharmacology of amphetamine

Amphetamine is a central nervous system (CNS) stimulant that causes hypertension and tachycardia with feelings of increased confidence, sociability and energy. It suppresses appetite and fatigue and leads to insomnia. Following oral use, the effects usually start within 30 minutes and last for many hours. Later, users may feel irritable, restless, anxious, depressed and lethargic. Amphetamine is less potent than methamphetamine, but in uncontrolled situations the effects are almost indistinguishable. It is rapidly absorbed after oral administration. After a single oral dose of 10 mg, maximum plasma levels are around 0.02 mg/l. The plasma half-life varies from 4 to 12 hours and is dependent on the urinary pH: alkaline urine decreases the rate of elimination. Analysis of amphetamine in urine is confounded because it is a metabolite of methamphetamine and certain medicinal products. Acute intoxication causes serious cardiovascular disturbances as well as behavioural problems that include agitation, confusion, paranoia, impulsivity and violence. Chronic use of amphetamine causes neurochemical and neuroanatomical changes. Dependence — as shown by increased tolerance — results in deficits in memory and in decision-making and verbal reasoning. Some of the symptoms resemble those of paranoid schizophrenia. These effects may outlast drug use, although often they resolve eventually. Fatalities directly attributed to amphetamine are rare. The estimated minimum lethal dose in non-addicted adults is 200 mg.

Source: EMCDDA drug profiles (http://www.emcdda.europa.eu/publications/drug-profiles).

Acute effects

Amphetamine

Laboratory studies investigating the effects of (dextro) amphetamine on the neurocognitive performance of non-fatigued healthy adults have found varying results. McKetin et al. (1999) found that 10 and 20 mg dextroamphetamine produced a dose–response increase in hit rate and a decrease in reaction time

without changing false alarm rate during a complex auditory selective attention task. Asghar et al. (2003) also found that the use of dextroamphetamine (25 mg) decreased reaction times. Dextroamphetamine (10 mg) enhances performance on single-target and divided-attention responses in different parts of the visual field (Mills et al., 2001). Another study found individual-specific effects of dextroamphetamine (0.25 mg/kg) on working memory, with improved performance in subjects who had relatively low working-memory capacity at baseline and deteriorated performance in subjects with high working-memory capacity at baseline (Mattay et al., 2000). Barch and Carter (2005) also observed that dextroamphetamine (0.25 mg/kg) has positive effects on cognitive function, namely improved reaction times on the spatial working memory and Stroop tasks, improved working-memory accuracy and improved language production. Silber et al. (2006) found that dextroamphetamine (0.42 mg/kg) improves various aspects of attention (reaction time during digit vigilance, DSST and movement estimation performance) and some aspects of psychomotor functioning (tracking ability) and perceptual speed (inspection time). Experimental studies on the effect of dextroamphetamine (10 and 20 mg) on impulsivity and decision-making found a decrease in several forms of impulsive behaviour, while alcohol (0.2, 0.4 and 0.8 g/l) resulted in the opposite effect (de Wit et al., 2000, 2002). Some laboratory studies, however, report negative acute effects of amphetamine on neurocognitive performance. Hutchison and Swift (1999) found that 20 mg dextroamphetamine causes subtle but significant negative effects on prepulse inhibition of the startle reflex, reflecting deficits in the ability to filter out irrelevant or intrusive stimuli, which subsequently causes an overload of information. This finding was confirmed by Swerdlow et al. (2003).

Silber et al. (2005) found, during tests in a driving simulator, that the intake of dextroamphetamine (0.42 mg/kg) causes a decrease in overall simulated driving performance by inducing problems such as incorrect signalling, failing to stop at a red traffic light and slow reaction times. The decrease in simulated driving ability was observed only during the daytime, which is consistent with the fact that amphetamine consumption results in tunnel vision, an effect that would be less apparent at night (Mills et al., 2001; Silber et al., 2005).

Other studies have assessed the effects of dextroamphetamine during sleep deprivation. Wesensten et al. (2005) investigated the effects of 20 mg dextroamphetamine on simple psychomotor tasks during sleep deprivation and found that it improved psychomotor vigilance speed relative to placebo. The effects of the drug on cognitive function during sleep deprivation are unclear. Mills et al. (2001) found that 10 mg of dextroamphetamine had no performance-enhancing effect, while Wesensten et al. (2005) observed improvement on some aspects of cognitive function (e.g. learning to learn on WCST) and impairment on others (e.g. performance on Stroop test) after administration of 20 mg dextroamphetamine. Magill et al. (2003) examined the effects of tyrosine (150 mg/kg), phentermine (37.5 mg), caffeine (300 mg/70 kg), dextroamphetamine (20 mg) or placebo on cognitive and motor performance in healthy young men during sleep deprivation. The substances were administered at 15.30 hours following overnight sleep deprivation. Performance decrements with sleep deprivation occurred in visual scanning, running memory, logical reasoning, mathematical processing, the Stroop test, the time wall test, tracking and visual vigilance. The statistical comparisons of task performances 1.5 and 5.5 hours after drug administration and at the 13.00 hours pre-drug baseline session showed that dextroamphetamine improved performance at both post-drug sessions on all but one task in which subjects had shown impairment due to sleep deprivation. The exception was in logical reasoning 1.5 hours post drug administration. However, this aspect of performance was significantly improved 5.5 hours after dextroamphetamine administration.

Jones and Holmgren (2005) presented a case series of individuals apprehended in Sweden for driving under the influence of drugs who had abnormally high concentrations of amphetamine in their blood (> 5.0 mg/l). The commonest signs of drug use reported by the arresting officers were bloodshot and glazed eyes, restlessness, talkativeness, exaggerated reflexes and slurred speech. Unsteady gait and dilated pupils were observed in some, but not all, individuals. In contrast, in another series of 338 apprehended drivers in whom only amphetamine was found (Musshoff and Madea, 2012) (median and maximum concentration 0.12 and 1.05 mg/l, respectively), the psycho-physical condition of the drivers in many cases suggested that they were under the influence of a centrally sedating substance. A relationship between concentration and effect could not be established. The apparent sedation is probably the consequence of sleep deprivation during an amphetamine binge and the after-effects of the drug.

Cox et al. (2008) observed that extended-release mixed amphetamine salts (Adderall XR) were associated with worsening of driving performance, or a drug rebound effect, relative to placebo 16–17 hours post ingestion (the drugs were given at 8 a.m.). The performance on a

virtual reality driving simulator and an on-road drive of 19 male adolescent drivers aged 17–19 years with attention-deficit hyperactivity disorder (ADHD) was compared after taking 30 mg of extended-release mixed amphetamine salts or placebo. In group comparisons, extended-release mixed amphetamine salts were not associated with significant worsening of simulator performance relative to placebo 17 hours post ingestion. However, inattentive on-road driving errors were significantly more common on extended-release mixed amphetamine salts relative to placebo at midnight ($p = 0.04$), suggesting a possible rebound effect.

Hjalmdahl al. (2012) found that administration of *d*-amphetamine does not compensate for impairment of driving caused by fatigue. The positive effects of 10 mg were not further improved when increasing the dose to 40 mg.

Kay et al. (2009) performed a randomised, double-blind, placebo-controlled, crossover study of simulated driving performance following administration of extended-release mixed amphetamine salts 50 mg/day in young adults with ADHD. Extended-release mixed amphetamine salts significantly improved overall simulated driving performance compared with placebo up to 12 hours after dosing.

An expert panel in Norway (Vindenes et al., 2012) proposed a cut-off value for amphetamine in blood of 41 ng/ml, corresponding to an alcohol concentration of 0.2 g/l.

Combinations of amphetamine with other substances

Simons et al. (2012) studied the combination of dexamphetamine and alcohol. Eighteen subjects participated in a randomised, crossover, placebo-controlled driving simulator study employing four conditions: 10 mg dexamphetamine, 0.8 g/kg alcohol, 10 mg dexamphetamine + 0.8 g/kg alcohol and placebo. Mean BAC levels during simulated driving varied between 0.64 g/l and 0.91 g/l depending on time after administration. In the subjects who consumed alcohol, mean SDLP was significantly higher and accepted gap time and distance were significantly lower ([3]). Use of alcohol or dexamphetamine plus alcohol was associated with a higher frequency of red light running and collisions than the dexamphetamine alone or placebo condition. Performance of vigilance and divided attention tasks was significantly impaired in the alcohol condition and, to a lesser degree, in the dexamphetamine + alcohol condition. The authors concluded that single doses of 0.8 g/kg alcohol increased risk-taking behaviours and impaired tracking, attention and reaction time during a 3-hour period after drinking when BAC declined from 0.9 to 0.2 g/l. The stimulatory effects of co-administration of dexamphetamine 10 mg were not sufficient to overcome the impairing effects of alcohol on skills related to driving.

Methamphetamine

In healthy volunteers, Comer et al. (2001) found no effect of 5 or 10 mg methamphetamine on the performance on a battery of tests consisting of a DSST, a repeated acquisition task, a divided attention task, a rapid information processing task and an immediate and delayed digit-recall task. Laboratory studies using higher doses did find acute effects on cognitive and psychomotor performance. Johnson et al. (2000) investigated the cognitive effects induced by *d*-methamphetamine ([4]) (0.21 or 0.42 mg/kg) in healthy volunteers. They found an increase in mean hits and decreases in mean false hits and mean reaction time on the RVIPT. On the logical reasoning test, *d*-methamphetamine significantly improved the percentage correct to time ratio. There was no effect on the FTT, a measure of motor speed. The same research group studied the effects of *d*-methamphetamine (15 and 30 mg) in methamphetamine-dependent individuals and found a dose-dependent increase in attention, concentration and psychomotor performance (Johnson et al., 2005, 2007). Silber et al. (2006) assessed the acute effects of 0.42 mg/kg *d*-methamphetamine and *d,l*-methamphetamine on driving-related cognitive functions in healthy volunteers. Both kinds of methamphetamine improved attention (digit vigilance, DSST and movement estimation), psychomotor performance (tracking ability) and perceptual speed (inspection time).

Silber et al. (2012a) administered 0.42 mg/kg *d*-methamphetamine or a matching placebo to 20 healthy recreational users of illicit stimulants. Performance was assessed 2.5 hours post drug administration. *d*-Methamphetamine did not significantly

([3]) Gap acceptance measures the driver's ability to safely traverse a crossing. The parameters included to assess risk taking are size of the accepted gap in seconds and the distance to the car approaching the driver while traversing the crossing.

([4]) There are three different types of methamphetamine (*d, d/l* and *l*), and each affects the CNS differently. The most common types are the dextro/laevo (*d/l*) and dextro (*d*) types. The most powerful is *d*-methamphetamine (3–4 times more powerful than *l*-methamphetamine).

Pharmacology of methamphetamine

Methamphetamine is a CNS stimulant that causes hypertension and tachycardia with feelings of increased confidence, sociability and energy. It suppresses appetite and fatigue and leads to insomnia. Following oral use, the effects usually start within 30 minutes and last for many hours. Later, users may feel irritable, restless, anxious, depressed and lethargic. Methamphetamine has higher potency than amphetamine, but in uncontrolled situations the effects are almost indistinguishable. It is rapidly absorbed after oral administration, and maximum plasma levels are in the range 0.001–0.005 mg/l. The plasma half-life is about 9 hours. Fatalities directly attributed to methamphetamine are rare. In most fatal poisonings the blood concentration is above 0.5 mg/l. Analysis of methamphetamine in urine is confounded because it is a metabolite of certain medicinal products (e.g. selegiline). Acute intoxication causes serious cardiovascular disturbances as well as behavioural problems that include agitation, confusion, paranoia, impulsivity and violence. Chronic use of methamphetamine causes neurochemical and neuroanatomical changes. Dependence — as shown by increased tolerance — results in deficits in memory and in decision-making and verbal reasoning. Some of the symptoms resemble those of paranoid schizophrenia. These effects may outlast drug use, although often they resolve eventually.

Source: EMCDDA drug profiles (http://www.emcdda.europa.eu/publications/drug-profiles).

impair overall simulated driving performance. Compared with placebo, the *d*-methamphetamine condition led to four times more infringements, i.e. failure to stop at red traffic lights, but this effect was evident only at a trend level ($p = 0.11$). In another study (Silber et al., 2012b), in 20 healthy recreational users of illicit stimulants, driving performance was assessed in two testing sessions 2.5 hours following oral administration of 0.42 mg/kg *d,l*-methamphetamine or a matching placebo. Mean blood and saliva *d,l*-methamphetamine concentrations of approximately 90 and 400 ng/ml, respectively, at 2 hours and 95 and 475 ng/ml at 3 hours were observed. These levels of *d,l*-methamphetamine were found not to significantly impair, or improve, driving performance.

Stough et al. (2012) gave 0.42 mg/kg methamphetamine or a matching placebo to 61 abstinent recreational users of illicit drugs. Driving performance was assessed 3 hours and 24 hours post drug administration on a computerised driving simulator. The methamphetamine condition impaired driving performance to a greater extent than placebo ($p = 0.055$). Signalling adherence was lower in those who received methamphetamine ($p = 0.006$) than in those receiving placebo in the daytime simulations.

Bosanquet et al. (2013) compared driving simulator performance in current methamphetamine users and a control group of non-users. Methamphetamine users, most of whom met the criteria for methamphetamine dependence, were significantly more likely to speed and to weave 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.

An expert panel in Norway (Vindenes et al., 2012) proposed a cut-off value for methamphetamine in blood of 45 ng/ml, corresponding to an alcohol concentration of 0.2 g/l.

MDMA

Laboratory studies have variously shown both negative and positive as well as no effects of MDMA on driving-related abilities. Cami et al. (2000) found that MDMA (75 mg or 125 mg) produced a mild decrease in responses in the DSST in healthy volunteers. Only the 125-mg dose induced esophoria in the Maddox wing device.

Hernandez-Lopez et al. (2002) investigated the effects of MDMA (100 mg) on psychomotor performance in healthy volunteers, but they found no effect on performance on the DSST, SRT or the Maddox wing device. MDMA (100 mg), given in two successive doses separated by an interval of 24 hours, was studied by Farré et al. (2004). In the DSST task, both doses slightly decreased the total number of DSST responses, but these changes were not significant. MDMA did not produce significant effects on reaction time. Both doses produced similar levels of esophoria in the Maddox wing device. In a study of recreational MDMA users, a single dose of MDMA (75 mg) was administered and cognition, psychomotor performance and driving-related task performance were assessed (Lamers et al., 2003). MDMA improved psychomotor performance, such as movement speed and tracking performance, in a single task as well as in a divided attention task. The ability to

Pharmacology of MDMA (ecstasy)

Ingestion of MDMA causes euphoria, increased sensory awareness and mild central stimulation. The terms 'empathogenic' and 'entactogenic' have been coined to describe the socialising effects of MDMA. Following ingestion, most of the dose of MDMA is excreted in the urine, unchanged. Following a dose of 75 mg, the maximum plasma concentration of around 0.13 mg/l is reached within 2 hours. The plasma half-life is 6–7 hours. In animals, MDMA causes neurotoxicity, as evidenced by anatomical changes in axon structure and a persisting reduction in brain serotonin levels. The significance of these findings to human users is still unclear, although cognitive impairment is associated with MDMA use. Some of the pharmacodynamic and toxic effects of MDMA vary, depending on which enantiomer is used. However, almost all illicit MDMA exists as a racemic mixture. Fatalities following a dose of 300 mg have been noted, but toxicity depends on many factors, including individual susceptibility and the circumstances in which MDMA is used.

Source: EMCDDA drug profiles (http://www.emcdda.europa.eu/publications/drug-profiles).

predict object movement under divided attention was impaired in the subjects. There was no effect of MDMA on visual search, planning or retrieval from semantic memory. Ramaekers et al. (2004) examined MDMA (75 mg) and cognition in recreational MDMA users. A single dose impaired performance on spatial and verbal working memory tasks 1.5 to 2.5 hours after administration. MDMA showed no effect on behavioural measures of impulsivity. Smith et al. (2006) conducted neuropsychological assessments in 13 MDMA users, 10–15 hours after last use and in a control group. The MDMA users showed impairments on measures of executive function and short-delay free recall memory. No extrapyramidal motor impairments were detected.

Tests in driving simulators revealed that the consumption of MDMA can decrease performance. De Waard et al. (2000) conducted driving simulator tests in a group of young people who had indicated that they regularly use MDMA. They were tested 1 hour after the consumption of MDMA, after the party, when the subject would normally go home, and then again while sober on a control night at a comparable time. Under the influence of MDMA, subjects drove faster, but only in built-up areas with a speed limit of 50 km/h. Speed variance also increased, both in the city and on the motorway. Lateral control and gap acceptance behaviour was not affected. There were two crashes during 20 control drives, and four crashes while under the influence of MDMA, a 100 % increase.

In another study of recreational MDMA users, subjects took a real on-the-road driving test 3–5 hours after consuming MDMA (75 mg) (Ramaekers et al., 2004). MDMA significantly decreased SDLP by 2 cm relative to placebo, and decreased performance during the car-following test. There were no effects on time to speed adaptation and BRT.

The doses given in the experimental studies on MDMA (75–125 mg) resemble the doses consumed by recreational MDMA users (average 120 mg) (Couper and Logan, 2004a).

Kuypers et al. (2007) assessed the effects of nocturnal doses of 75 and 50 mg MDMA divided over the evening on psychomotor performance and impulsivity during the night and after a night of sleep deprivation in 14 healthy subjects in a double-blind, placebo-controlled, two-way, within-subject study. MDMA impaired tracking performance in a simple tracking task. Divided attention task performance was also impaired. MDMA did not affect impulsivity measures. Vigilance performance decreased as a function of time on task, but this decrement was less during MDMA treatment than with placebo. After the administration of MDMA, the sleepiness scale scores were lower during the night, and this difference disappeared in the morning.

In a simulated car-following task, Dastrup et al. (2010) observed that, although all participants drove at approximately 90 km/h, 'drivers who had recently consumed MDMA maintained a shorter distance to the lead vehicle (mean 64 m) and responded to changes in the velocity of the lead vehicle more quickly (mean difference in delay 1.04 seconds) than other driver groups. Abstinent MDMA users also drove closer to the lead vehicle than control subjects, but reacted quickly to the changes in the velocity of the lead vehicle. The authors concluded that MDMA users' driving performance is no worse than that of control subjects but that they may take more risks. In a simulator study, Stough et al. (2012) administered 100 mg MDMA to 61 abstinent recreational users of illicit drugs. Driving performance was assessed 3 hours and 24 hours post drug administration. Performance in the MDMA condition was worse than in either the methamphetamine ($p = 0.023$) or the placebo ($p < 0.001$) condition, and methamphetamine was also

observed to result in a deterioration in driving ability compared with placebo ($p = 0.055$). Those administered MDMA demonstrated poorer signalling adherence ($p = 0.017$) conditions than those administered placebo in the daytime simulations.

Bosker et al. (2012b) assessed the effects of MDMA on road-tracking and car-following performance in on-the-road driving tests in normal traffic in 16 recreational MDMA users. Participants received a single dose of 0, 25, 50 or 100 mg MDMA on separate evenings. The driving tests were conducted both in the evening, when MDMA serum concentrations were maximal, and in the morning, after a night without sleep. SDLP was significantly increased during driving tests in the morning in all treatment conditions, irrespective of MDMA dose administered and serum concentration at the time of testing. The increments in SDLP were of high clinical relevance and comparable to those observed for alcohol at BACs > 0.8 g/l. This impairment was primarily caused by sleep loss. MDMA did not affect driving performance nor did it change the impairing effects of sleep loss. MDMA cannot compensate for the impairing effects of sleep loss; drivers who are under the influence of MDMA and are sleep deprived are unfit to drive.

In the DRUID meta-analysis of experimental studies (Berghaus et al., 2010), 10 studies examining 208 effects of *d*-amphetamine were analysed. The doses used varied between 1 and 36 mg. At the highest dose range (> 7.5 mg), the maximal percentage of significantly impaired test results was 0 %. The time of maximal impairment and the duration of impairment could not be determined as there was no impairment. The alcohol equivalence of maximum impairment was < 0.3 g/l. The equivalent BAC (0.5 g/l) was not reached.

An expert panel in Norway (Vindenes et al., 2012) proposed a cut-off value of 48 ng/ml for MDMA in blood of 48 ng/ml, corresponding to an alcohol concentration of 0.2 g/l.

Combination of MDMA with other psychoactive substances

Hernandez-Lopez et al. (2002) investigated the effects of MDMA (100 mg) with or without alcohol (0.8 g/l) on psychomotor performance in healthy volunteers. The combination of alcohol and MDMA produced a similar impairment to that of alcohol alone in scores on the DSST, but a significant decrease in the number of total and correct responses compared with placebo and MDMA. MDMA partially reversed the exophoria induced by alcohol in the Maddox wing test. SRT was significantly increased by the combination of MDMA and alcohol, but not by alcohol alone or MDMA alone. Brookhuis et al. (2004) asked a group of young participants who had indicated that they regularly used MDMA to complete test rides in a driving simulator shortly after having used MDMA, just before going to a party. They were tested again after having visited the 'rave', while they were under the influence of MDMA and a number of other drugs, and then again when they were sober, at around the same time of night. Separately, a control group of participants was included in the experiment. Driving performance in terms of lateral and longitudinal vehicle control was not greatly affected after MDMA use but deteriorated after multiple drug use. The most striking result was the apparent decrease in risk awareness, both after taking MDMA and after multiple drug use, as was shown by the significantly smaller accepted gaps than in the non-drug condition. Accident involvement was increased by 100 % and 150 % after MDMA use and multiple drug use, respectively. However, Ramaekers et al. (2004) found that the use of MDMA (75 mg or 100 mg) can diminish some, but not all, deleterious effects of alcohol (0.5–0.6 g/l), while other negative effects of alcohol can be reinforced.

Dumont et al. (2008) studied the acute effects of individual and co-administration of MDMA and ethanol on executive, memory and psychomotor, visuomotor, visuospatial and attention function, as well as on subjective experience, in 16 healthy volunteers between the ages of 18 and 29 years. MDMA was given orally (100 mg) and BAC was maintained at 0.6 g/l by an ethanol infusion regime. Co-administration of MDMA and ethanol was well tolerated and did not result in greater impairment of performance than the single-drug conditions. Impaired memory function was consistently observed after all drug conditions, whereas impairment of psychomotor function and attention was less consistent across drug conditions. In another study by the same group (Dumont et al., 2010), MDMA significantly increased psychomotor speed but did not affect psychomotor accuracy and induced subjective arousal. Ethanol impaired both psychomotor speed and accuracy and induced sedation. Co-administration of ethanol and MDMA improved psychomotor speed but impaired psychomotor accuracy compared with placebo and reversed ethanol-induced sedation. Maximal effects were seen at 90–150 minutes after MDMA administration, after which drug effects declined in spite of persisting MDMA plasma concentration, with the exception of ethanol-induced sedation, which manifested itself fully only after the infusion was stopped.

Dumont et al. (2011) performed a four-way, double-blind, randomised, crossover, placebo-controlled study in 16

healthy volunteers between the ages of 18 and 27 years. MDMA (100 mg) was given orally and THC (4 and 12 mg, given at intervals of 90 minutes) was vaporised and inhaled. THC induced more robust cognitive impairment than MDMA and co-administration did not exacerbate single-drug effects on cognitive function. However, co-administration of THC with MDMA increased desired subjective drug effects and drug strength compared with the MDMA condition, which may explain the widespread use of this combination. Veldstra et al. (2012) studied driver impairment as a consequence of ecstasy or combined ecstasy and alcohol use as compared with driving under the influence of 0.3 g/l, 0.5 g/l and 0.8 g/l alcohol. Alcohol and ecstasy mainly influenced automated driving performance such as lateral and speed control. However, small to no effects of the substances were found on more complex driving behaviour. Equivalence testing showed that combined use may lead to impaired driving in some, but not all, drivers. Participants rated their own performance to be only slightly worse than normal in both studies. Since driving performance, in fact, deteriorated significantly, participants overestimated their own ability.

Duration of effects of amphetamines

The effects on cognitive and psychomotor skills of amphetamine (Asghar et al., 2003; Barch and Carter, 2005; de Wit et al., 2000, 2002; Hutchison and Swift, 1999) and methamphetamine (Johnson et al., 2000, 2005, 2007; Silber et al., 2006) have been assessed for up to 3–4 hours after administration. With MDMA use, the duration of the subjective 'positive' effects is less than 24 hours; thereafter, the 'crash' phase starts, with the subject feeling very tired, unable to combat sleep and even depressed, which can last for several days (Verheyden et al., 2003). These negative after-effects increase with successive doses, while the positive subjective effects diminish (Hegadoren et al., 1999). The effects on psychomotor performance can last for more than 5 hours (Lamers et al., 2003). The duration of the cognitive effects is unclear. Some studies have found that the negative effects on cognitive performance, especially verbal memory, can last for several days (Smith et al., 2006), while others have found that impairment disappears after a few hours (Farré et al., 2004) or 24 hours after the last use (de Waard et al., 2000).

Chronic effects

Experimental studies of the chronic effects of amphetamine use have shown deficits in decision-making, attention and memory (McKetin and Solowij, 1999; Ornstein et al., 2000; Rapeli et al., 2005; Rogers et al., 1999). Some of these deficits are correlated with increasing years of use (Rogers et al., 1999) or increasing severity of use (McKetin and Solowij, 1999). Rapeli et al. (2005), however, found that attention deficits of recently detoxified amphetamine users may be reversible, although recovery of verbal memory is not complete even after long-term abstinence. The chronic effects associated with the use of methamphetamine are deficits in memory, attention, response inhibition and psychomotor speed and an increase in impulsivity (Chang et al., 2002; Chou et al., 2004; Hoffman et al., 2006; Johanson et al., 2006; Monterosso et al., 2005; Newton et al., 2004; Salo et al., 2002, 2005; Simon et al., 2000; Volkow et al., 2001). Some of these deficits might persist even after a long period of abstinence (Chang et al., 2002; Hoffman et al., 2006; Johanson et al., 2006; Salo et al., 2002, 2005; Volkow et al., 2001), while others can be reversed after a short period of abstinence (Chou et al., 2004).

MDMA users are aware of the consequences of their chronic use and report the development of tolerance and impaired ability to concentrate (Verheyden et al., 2003). In experimental studies, the consequences of chronic amphetamine or MDMA use on cognitive functions include a decrease in executive functioning, attention and memory and an increased impulsivity. Some of these impairments become more prominent with increasing severity of use, and might persist for up to 2 years after the last use of the drug (Gouzoulis-Mayfrank et al., 2000; McCann et al., 1999; Quednow et al., 2007; Rizzo et al., 2005; Verdejo et al., 2004; Wareing et al., 2004).

Risks

In Norway, Gustavsen et al. (2006) investigated the concentration–effect relationship between blood amphetamine concentrations and impairment in a population of real-life users. They selected 878 cases with amphetamine or methamphetamine as the only drug present in blood samples from the impaired driver registry of the Norwegian Institute of Public Health. In each case, the police physician had determined whether or not the driver was impaired; 27 % were judged not impaired, while 73 % were judged impaired. A positive relationship was found between blood amphetamine concentration and impairment, but it reached a ceiling at concentrations of 270–530 ng/ml.

Accident involvement

Of the four pre-2007 epidemiological studies investigating the accident risk associated with driving

under the influence of amphetamines, three studies — one in France (Mura et al., 2003) and the Immortal studies in the Netherlands and Norway (Assum et al., 2005) — could not calculate the risks because the number of cases positive for amphetamines was too low. The fourth, a study in Canada, found that driving under the influence of amphetamines is associated with an increased accident risk of 12.8 (OR; 95 % CI 3.0–54.0) (Dussault et al., 2002).

Based on the DRUID results from Belgium (Kuypers et al., 2012), only a crude OR could be calculated: 54.82 (95 % CI 6.09–493.12). For the combination of alcohol and stimulants, the adjusted OR was 20.34 (95 % CI 4.93–83.82), and for the combination of stimulants and sedatives the adjusted OR was 210.97 (95 % CI 4.90–9089).

In the DRUID case–control study (Hels et al., 2011), the relative risk of serious injury when driving under the influence of amphetamines was estimated to be greatly increased (5–30). The adjusted OR, based on data for all countries, was 8.35 (95 % CI 3.91–17.83) for serious injury and 24.09 (95 % CI 9.72–59.71) for death.

All these studies show that driving under the influence of amphetamines caries a high accident risk.

Responsibility analyses

Drummer et al. (2004) conducted a responsibility analysis among 3 398 fatally injured drivers. They calculate the risks associated not with amphetamines alone, but with a group of substances acting as stimulants, namely amphetamine, methamphetamine, MDMA, ephedrine, pseudoephedrine, phentermine and cocaine. There was no significant association between stimulants use and crash responsibility. However, when truckers were considered as a discrete driver type, the OR increased to 8.8 and was of borderline statistical significance (95 % CI 1.0–77.8). In the other study in Australia, Longo et al. (2000b) also calculated the risks associated with a group of substances acting as stimulants, but these included amphetamine, methamphetamine, phentermine, pseudoephedrine, ephedrine and MDEA. They found that there was no significantly increased responsibility risk associated with driving under the influence of stimulants alone.

Two studies looked at the responsibility risk associated with amphetamines only. In Canada, Dussault et al. (2002) found that driving under the influence of amphetamines is associated with an infinite risk of responsibility for an accident. This is probably caused by the fact that only a limited number of fatally injured drivers tested positive for amphetamines and that all these drivers were judged responsible for the accident. A responsibility analysis in France found amphetamines to be associated with an increased risk of responsibility for an accident (OR 3.8; 95 % CI 1.5–9.5) (Laumon et al., 2005). However, after adjustment for confounding factors such as age, sex, vehicle type and time of crash, the increase in risk was no longer significant (OR 2.0; 95 % CI 0.7–5.3).

The relationship between amphetamine use and the severity of a traffic accident was examined in one epidemiological study. In the Netherlands, Smink et al. (2005) analysed blood sample data from drivers involved in crashes from October 1998 to September 1999. The blood samples had been screened for the presence of alcohol, illicit drugs and medicinal drugs. The strength of the association between exposure to the different classes of substances and the severity of the accident was evaluated using logistic regression analysis. The results showed no association between the use of amphetamines and amphetamine-like substances and the severity of a traffic accident.

Meta-analysis

Elvik (2013) performed a meta-analysis of 66 publications. The best estimate of the relative risk of accident involvement with amphetamine, adjusted for publication bias, was 4.46 (95 % CI 2.21–9.00) for fatal accidents, 6.19 (95 % CI 3.46–11.06) for injury accidents and 8.67 (95 % CI 3.23–23.32) for crashes resulting in property damage.

Conclusion

Acute effects: Experimental studies show that methamphetamine and amphetamine can have positive stimulating effects on cognitive and psychomotor functions, especially in fatigued or sleep-deprived persons. Negative effects are also observed, such as an overall reduced driving capacity in a simulator during daytime. Stimulants have repeatedly been shown to improve neuropsychological skills, such as tracking, impulse control and reaction time, while impairing cognitive functions such as working memory and movement perception. However, the doses used in these studies are not representative of the doses actually consumed by users of these drugs. High-dose effects of stimulants on driving performance cannot be readily assessed in experimental, placebo-controlled studies because of obvious medical and ethical constraints.

MDMA and amphetamine concentrations that are observed in actual cases of driving under the influence can be 10-fold higher than during controlled administration in experimental studies. Individuals who take stimulants alone at regular doses (e.g. as in medicinal use) are generally fit to drive, but are less safe drivers when stimulants are taken in combination with sleep loss or alcohol intoxication, as is often the case in drug users. Neither MDMA nor dexamphetamine produces any dose- or concentration-related effects on driving (Ramaekers et al., 2012). Experimental studies of MDMA have also found both negative and positive effects on performance. Positive effects include a decrease in SDLP and an increase in psychomotor speed, while negative effects include an increase in speed and speed variance and a decrease in the ability to follow a car.

Duration of effects: The effects on psychomotor performance can last for more than 5 hours, and some studies have shown that the negative effects on cognitive performance, especially verbal memory, can last for several days.

Combinations: Other psychoactive substances such as alcohol can reinforce the deleterious effects of MDMA, and even have some additional negative effects. The use of MDMA or amphetamine can diminish some, but not all, deleterious effects of alcohol, while other negative effects of alcohol can be reinforced. In addition, neither stimulant can compensate for the impairing effects of alcohol and sleep deprivation even at high doses or concentrations. There was a large variation in subjects' sensitivity to the combination of amphetamine and alcohol or MDMA and alcohol; some showed impairment, whereas others did not.

Chronic use: The chronic use of amphetamines causes negative effects on cognitive and psychomotor skills, and these last longer than the period of intoxication and are sometimes correlated with the severity or duration of use.

Threshold concentration: An expert panel in Norway proposed that, for the purposes of sanctions, concentrations in blood of 41 ng/ml amphetamine, 45 ng/ml methamphetamine and 48 ng/ml MDMA should be considered equivalent to an alcohol concentration of 0.2 g/l. Limits equivalent to higher BACs have not been suggested because the correlation between drug concentration and risk of traffic accidents/impairment is variable or insufficiently documented. Marked impairment can be seen at low concentrations of some substances, such as amphetamine and methamphetamine, particularly some time after substantial drug intake.

Accident risk: Meta-analyses on the risks associated with the use of amphetamines have shown high odds ratios. Based on a meta-analysis, the relative risk of accident involvement with amphetamine was 4.46 (95 % CI 2.21–9.00) for fatal accidents, 6.19 (95 % CI 3.46–11.06) for injury accidents and 8.67 (95 % CI 3.23–23.32) for crashes resulting in property damage.

Cocaine

Acute effects

Only two experimental studies of the acute effects of cocaine on performance were found. Rush et al. (1999) administered a wide range of doses of oral cocaine (50, 100, 200 and 300 mg) or placebo to nine volunteers with recent histories of cocaine use. Their performance on the DSST was assessed before drug administration and periodically afterwards for 5 hours. Performance was not affected in this study, although previous studies found performance-enhancing effects with acute administration. Rush et al. (1999) remarked that the subjects in the previous studies reported substantially less cocaine use than the subjects in their study, who

Pharmacology of cocaine

Cocaine has a similar psychomotor stimulant effect to that of amphetamine and related compounds. Like amphetamine, it produces euphoria, tachycardia, hypertension and appetite suppression. Cocaine has a strong reinforcing action, causing a rapid psychological dependence, an effect even more pronounced in those who smoke cocaine base. Following a 25-mg dose, blood levels peak in the range 400–700 µg/l, depending on the route of administration. When consumed with alcohol, cocaine also produces the metabolite cocaethylene. Some unchanged cocaine is found in the urine. The plasma half-life of cocaine is 0.7–1.5 hours and is dose dependent. The estimated minimal lethal dose is 1.2 g, but susceptible individuals have died from as little as 30 mg applied to mucous membranes, whereas addicts may tolerate up to 5 g daily.

Source: EMCDDA drug profiles (http://www.emcdda.europa.eu/publications/drug-profiles).

may have developed tolerance to cocaine's performance-enhancing effects. Furthermore, the route of administration was oral in their study (producing a smaller effect and a slower onset of effects) while in one of the previous studies it was intranasal.

A study by Hopper et al. (2004) found no effect of a low dose of cocaine (0.2 mg/kg) on measures of attention, recall or recognition task performance. As acute cocaine administration can induce hypercortisolaemia (associated with symptoms such as mania, depression, poor concentration and hyperactivity), the researchers also investigated the effects of cortisol on performance. A low dose of cortisol (0.2 mg/kg) enhanced and a high dose (0.5 mg/kg) impaired vigilance attention, and a trend was found for the same dose–response profile on twice-heard words. An opposite trend was observed for recognition: cortisol at a low dose impaired and at a high dose enhanced recognition of once-heard words, and a very weak trend was found for recognition of new words. The authors concluded that these results should be interpreted with caution, given several methodological limitations (e.g. the low dose of cocaine), but that these findings suggest that the effects of cocaine can be influenced by the induction of hypercortisolaemia.

An expert panel in Norway (Vindenes et al., 2012) proposed that, for the purposes of sanctions, a cut-off value for cocaine in blood of 24 ng/ml should be considered equivalent to an alcohol concentration of 0.2 g/l.

Combination with other psychoactive substances

No experimental studies on the effects of the combination of cocaine with another psychoactive substance were found that were published in 1999 or later. Therefore, a short overview will be given of studies published before 1999.

These studies show that cocaine can partially diminish performance impairments caused by alcohol consumption. The use of a combination of alcohol and cocaine decreases psychomotor impairment and improves performance on cognitive tests when compared with the use of alcohol alone (Farré et al., 1993; Foltin et al., 1993). Cocaine use also reduces the subjective feeling of drunkenness caused by alcohol (Farré et al., 1993; Foltin et al., 1993). The combined use of cocaine (96 mg cocaine hydrochloride) and cannabis (2.7 % THC) can cause additional performance decrements that are not caused by either drug alone, such as impaired performance on a repeated acquisition task (Foltin et al., 1993).

Chronic effects

Chronic use of cocaine can cause deficiencies in users, such as difficulties in processing cognitive tasks concerning attention, visuospatial perception, memory, cognitive flexibility, perceptual–motor speed, problem-solving, abstraction and executive functioning (Di Sclafani et al., 2002; Goldstein et al., 2004; Kelley et al., 2005; Lawton-Craddock et al., 2003; Rahman and Clarke, 2005; Smelson et al., 1999; Toomey et al., 2003). One study found no effects on attention or spatial memory (Kelley et al., 2005). Chronic cocaine use is also associated with an effect on behaviour, namely an increase in impulsive behaviour (Moeller et al., 2004).

Chronic use of alcohol or cocaine selectively affects performance on different neurobehavioural tests in a dose-dependent way (Bolla et al., 2000). However, their combined use may not cause additional negative effects on the brain, as subjects addicted to only cocaine demonstrate similar or greater neurocognitive impairments than those who abuse both alcohol and cocaine (Di Sclafani et al., 2002; Lawton-Craddock et al., 2003; Robinson et al., 1999).

Risks

Accident risk

Four epidemiological studies on the accident risk associated with driving under the influence of cocaine were found. However, three of these studies — one in France (Mura et al., 2003) and the Immortal studies in the Netherlands and Norway (Assum et al., 2005) — could not calculate the risks because the number of cases positive for cocaine was too low. A study in Canada (Dussault et al., 2002) found that driving under the influence of cocaine is associated with an increased accident risk of 12.2 (OR; 95 % CI 7.2–20.6). Driving under the influence of cocaine alone, a combination of cocaine and cannabis, a combination of cocaine and alcohol (BAC > 0.8 g/l) or a combination of cocaine, cannabis and alcohol (BAC > 0.8 g/l) was associated with an increased accident risk of 4.9 (OR; 95 % CI 1.4–17.4), 8.0 (OR; 95 % CI 3.1–20.7), 170.5 (OR; 95 % CI 21.2–1371.2) and 85.3 (OR; 95 % CI 9.5–767.0), respectively.

Stoduto et al. (2012) examined the association between self-reported past-year cocaine use and past-year collision involvement in a large representative sample of adult drivers in Ontario, Canada. The prevalence of self-reported collision involvement within the past year

was 18.9 % among those who used cocaine, compared with 7.4 % among non-users. Logistic regression analysis, controlling for the potential confounding effects of age, sex, income, driving exposure and drinking–driving measures, found that the odds of collision involvement in the preceding year among cocaine users was over twice that of non-users (OR 2.11; 95 % CI 1.06–4.18). In another study (Pulido et al., 2011b) of 17 484 car or motorcycle drivers in 2005 in Spain, logistic regression was used to adjust for distance driven and potential confounders. Cocaine use on 1 day or more a week was associated with more traffic injuries (OR 2.8; 95 % CI 1.1–7.1).

Responsibility analyses

Drummer et al. (2004), in their responsibility analysis of 3 398 fatally injured drivers, calculated the risks associated with driving under the influence not of cocaine alone, but of a group of substances acting as stimulants, namely amphetamine, methamphetamine, MDMA, ephedrine, pseudoephedrine, phentermine and cocaine. There was no significant association between stimulant use and crash responsibility, except for the subset of truckers, in which case the OR increased to 8.8 and was of borderline statistical significance (95 % CI 1.0–77.8). Dussault et al. (2002) investigated the contribution of alcohol and other drugs in fatal crashes in Québec, Canada. They found that driving under the influence of cocaine alone, or in combination with cannabis and/or alcohol, is associated with an infinite risk of responsibility for an accident. This is probably because only a limited number of fatally injured drivers tested positive for cocaine and because all these drivers were judged responsible for the accident. A responsibility analysis in France found that driving under the influence of cocaine is associated with an increased risk of responsibility for an accident (OR 4.4; 95 % CI 1.0–19.0) (Laumon et al., 2005). However, after adjustment for confounding factors such as age, sex, vehicle type and time of crash, the increase in risk was no longer significant (OR 4.2; 95 % CI 0.9–19.6). Soderstrom et al. (2005) found that drivers under the influence of cocaine are significantly more likely to be responsible for a crash than drivers who are not under the influence of this drug (OR 2.3; 95 % CI 1.4–4.0).

Based on the DRUID results in Belgium (Kuypers et al., 2012), only a crude OR could be calculated: 6.85 (95 % CI 0.62–75.94) for cases in which only benzoylecgonine was found and 2.74 (95 % CI 0.32–23.59) for cases in which cocaine was found. For the combination of alcohol and stimulants, the adjusted OR was 20.34 (95 % CI 4.93–83.82), and for the combination of stimulants and sedatives the adjusted OR was 210.97 (95 % CI 4.90–9089).

In the DRUID case–control study (Hels et al., 2011), the relative risk of incurring serious injury when driving under the influence cocaine was estimated to be increased to a middling degree (RR 2–10). The adjusted OR, based on data for all countries, was 3.30 (95 % CI 1.40–7.79) for cocaine and serious injury and 3.70 (95 % CI 1.60–8.57) for benzoylecgonine and death.

One epidemiological study investigated the relationship between cocaine use and the severity of a traffic accident. Smink et al. (2005) examined data from a group of drivers who were involved in accidents in the Netherlands from October 1998 until September 1999. All blood samples had been screened for the presence of alcohol, illicit drugs and medicinal drugs. Logistic regression analysis showed no association between the use of cocaine and the severity of the accident.

Meta-analysis

In the meta-analysis of 66 publications by Elvik (2013), the best estimate of the relative risk of accident involvement with cocaine, adjusted for publication bias, was 2.96 (95 % CI 1.18–7.38) for fatal accidents, 1.66 (95 % CI 0.91–3.02) for injury accidents and 1.44 (95 % CI 0.93–2.23) for crashes resulting in property damage.

Conclusion

Acute effects: Few recent experimental studies exist on the acute effects of cocaine, and these are mostly restricted by methodological limitations, such as the administration of low doses of cocaine. The results of the few studies that were found suggest that the effects of cocaine can be influenced by the induction of hypercortisolaemia.

Duration of effects: Snorting cocaine produces effects almost immediately, and the resulting high may last 15–30 minutes. General effects will persist for 1–2 hours depending on the dose, and late-phase effects following binge use may last several days.

Combinations: Accident risk is higher when cocaine is used in combination with another psychoactive substance, such as alcohol and/or cannabis. Cocaine can partially reverse some negative effects of alcohol, while detrimental effects of other drugs such as cannabis can be reinforced. The chronic use of cocaine

can lead to cognitive defects, impaired psychomotor performance and impulsive behaviour.

Chronic use: Chronic use of cocaine can cause difficulties in processing cognitive tasks requiring attention, visuospatial perception, memory, cognitive flexibility, perceptual–motor speed, problem-solving, abstraction and executive functioning and an increase in impulsive behaviour.

Threshold concentration: An expert panel in Norway proposed a cut-off value for cocaine in blood of 24 ng/ml corresponding to an alcohol concentration of 0.2 g/l. Limits equivalent to higher BACs have not been suggested because the correlation between drug concentration and risk of traffic accidents/impairment is variable or insufficiently documented.

Accident risk: Epidemiological studies show that cocaine may increase the risk of being involved in or responsible for an accident. A meta-analysis showed that the relative risk of accident involvement with cocaine is 1.5 to 3.

Benzodiazepines and other medicines

Benzodiazepines (anxiolytics and hypnotics)

Benzodiazepines are used primarily for rapid relief of anxiety and for muscle relaxation, sedation and anticonvulsant effects. Chemically, these substances consist of a benzene ring fused with a diazepine ring which has a substituted benzene ring on its fifth position. Most structures resemble the 1,4-benzodiazepine skeleton; however, there are also 1,5-benzodiazepine derivatives (e.g. clobazam). The first benzene ring is sometimes substituted by a heteroaromatic system (e.g. clotiazepam). Benzodiazepines bind to the gamma-aminobutyric acid (GABA) receptor $GABA_A$, where they exert their pharmacological effect. In contrast to the barbiturates, they modulate the effects of the neurotransmitter GABA. In the absence of GABA, chloride channels do not open in the presence of benzodiazepines but they do with barbiturates, which may explain the narrow therapeutic window of the latter. Benzodiazepines tend to be safe in overdose when taken alone. When combined with other substances, especially alcohol, lethality is increased. At therapeutic doses, benzodiazepines do not suppress respiration in healthy individuals. They exert only minor effects on the cardiovascular system. Adverse effects most frequently encountered are impairment of mental and motor functions, drowsiness and light-headedness.

The 1,5-benzodiazepine derivatives are thought to be somewhat less sedating.

Depending on the metabolic pathway, benzodiazepines are divided into three groups:

- short-acting: triazolam and midazolam;
- medium-acting: alprazolam, bromazepam, brotizolam, clotiazepam, loprazolam, lorazepam, lormetazepam, oxazepam and temazepam;
- long-acting: clobazam, clonazepam, clorazepate, cloxazolam, diazepam, ethyl loflazepate, flunitrazepam, flurazepam, nitrazepam, nordazepam, prazepam and tetrazepam.

The short-acting benzodiazepines generally do not produce a 'hangover' effect if taken at bedtime. If the drug is stopped after a prolonged period of use, withdrawal symptoms occur; these can be quite severe, especially with the short- and medium-acting substances.

The newer benzodiazepine-like drugs (zolpidem, zaleplon and zopiclone, collectively called Z-hypnotics) were thought less likely to lead to dependence, although recent evidence suggests that they are no different from the benzodiazepines.

Effects

Table A8 (Appendix) summarises the results of experimental studies on benzodiazepines.

Short-acting benzodiazepines and benzodiazepine-like drugs

Danjou et al. (1999) compared the residual effects of administering zaleplon (10 mg), zolpidem (10 mg) or placebo 2–5 hours before awakening. A battery of tests (including CRT, DSST, CFF and LARS) were conducted 15 minutes after the subjects' morning awakening. Zaleplon showed no residual effect at any time at any point, whereas zolpidem's effects were still apparent up to 5 hours after administration. The effects of zolpidem lasted longer with this night-time administration than in previous studies using daytime administration, according to the authors.

A comparison of zaleplon (10 or 20 mg), zolpidem (10 or 20 mg), placebo and triazolam (0.25 mg) revealed no changes in memory or learning 1.25 hours and 8.25

hours after administration of zaleplon 10 mg (Troy et al., 2000). At the 1.25-hour mark, zolpidem 10 mg produced greater psychomotor impairment than the other substances. At 8.25 hours, cognitive impairment persisted in those administered zolpidem 20 mg and triazolam 0.25 mg.

Hindmarch et al. (2001a) administered zolpidem (10 mg) or zaleplon (10 or 20 mg) at night-time, 5 hours, 3 hours and 1 hour before awakening at 8.00 a.m., at which time tests were conducted (including CFF, CRT, DSST and LARS). Zaleplon 10 mg did not produce any effects, except a small effect on the DSST score 1 hour after administration. Zaleplon 20 mg led to significant residual effects on memory and performance 1 hour after administration. Zolpidem had residual effects on DSST and Sternberg memory scanning for up to 3 hours following administration, and an effect on CRT and delayed free recall of words that lasted up to 5 hours after administration. Zolpidem 10 mg showed more residual effects than zaleplon 20 mg.

In another night-time administration study, Verster et al. (2002a) examined the effects of zaleplon (10 or 20 mg) and zolpidem (10 or 20 mg) on driving ability, memory and psychomotor performance. Driving ability was assessed 4–5 hours after drug administration. Zaleplon did not affect performance, whereas zolpidem did so in a dose-dependent manner.

Although zaleplon generally does not impair driving, a case report by Stillwell (2003) shows the contrary. The subject, whose blood concentration of zaleplon was 0.13 µg/ml, showed symptoms of slow movements and reactions, and poor coordination and lack of balance. The author concluded that higher than therapeutic blood concentrations of zaleplon have the potential to cause impairment of psychomotor functions. Logan and Couper (2001) concluded the same for zolpidem. Whether zolpidem was used alone or in combination with other drugs, the symptoms generally were the same. Zolpidem levels in subjects' blood ranged from 0.08 to 1.4 mg/l. Even levels consistent with normal therapeutic concentrations have the potential to affect driving ability.

Mintzer and Griffiths (2007) studied the effects on memory tasks of triazolam (0.25 or 0.5 mg/70 kg) alone, *d*-amphetamine sulphate (20 or 30 mg/70 kg) alone, or their combination. Relative to the sedative measures, *d*-amphetamine showed less reversal of triazolam's effects on the memory measures. The memory measures ranged in degree of reversal: the most reversal was observed for reaction time on the n-back working memory task and the least reversal for accuracy on the Sternberg working memory task.

An overview of the pharmacodynamic profile of zaleplon is given by Patat et al. (2001). In young adults, the recommended dose of zaleplon, 10 mg, produced minimal or no impairment of psychomotor function and memory performance even when administered at night as little as 1 hour before awakening. No impairment of actual driving was observed when zaleplon 10 mg was administered either at bedtime or in the middle of the night as little as 4 hours before awakening. Zaleplon 20 mg generally produced significant impairment of performance and cognitive functions when these functions were measured at the time of peak plasma concentration (1 hour after dose administration), and no impairment of driving abilities when measured 4 hours after a middle-of-the-night administration.

A single oral dose of zolpidem (5, 10 or 20 mg/70 kg) or triazolam (0.125, 0.25 or 0.5 mg/70 kg) produced similar dose-related effects on memory for target information (Mintzer and Griffiths, 1999). The results suggested that triazolam, but not zolpidem, impaired memory for the screen location of picture stimuli.

Greenblatt et al. (2005) compared the effects of triazolam 0.375 mg on EEG and the DSST. The changes for the measures are highly correlated.

Vermeeren et al. (2002a) examined the effects of alcohol (0.3 g/l), zaleplon (10 mg) or zopiclone (7.5 mg). A highway driving test was performed 40 minutes after administration of alcohol and 10 hours after administration of zaleplon or zopiclone. Zopiclone and alcohol each produced marked impairment, with the magnitude of impairment with zopiclone being twice that with alcohol. Zaleplon produced no impairment.

Bocca et al. (2011) administered zopiclone (7.5 mg), zolpidem (10 mg), flunitrazepam (1 mg) as a positive control or a placebo at each subject's home at 11.00 p.m. The next morning, at 9.00 a.m., the subjects were asked to drive in a simulated monotonous driving environment for 1 hour. In comparison with placebo, zopiclone and zolpidem equivalently and significantly increased the SDLP, the standard deviation of speed and the number of road exits.

Gustavsen et al. (2009) found a strong relationship between zopiclone concentration and effect on both driving ability and control behaviours, and a weaker relationship between zopiclone concentration and effect on executive planning behaviour. Significant impairment (of automotive and control behaviour) was first observed

at zopiclone concentrations above 16 µg/l. Acute tolerance was found.

Leufkens and Vermeeren (2009) evaluated the residual effects of evening doses of temazepam 20 mg and zopiclone 7.5 mg on driving in healthy elderly drivers. Participants performed a standardised highway driving test between 10 and 11 hours after drug administration. Temazepam 20 mg was unlikely to impair driving 10 hours or more after bedtime administration in healthy elderly persons aged 65–75 years. Zopiclone 7.5 mg moderately impaired driving in the elderly for at least 11 hours after administration. The magnitude of impairment in the elderly was similar to that found previously in younger volunteers.

Mets et al. (2011) found a significant increase in SDLP (+ 2.9 cm) in healthy adult subjects the morning after administration of 7.5 mg zopiclone. Zopiclone also significantly impaired driving performance, cognitive, memory and psychomotor performance the morning after bedtime administration.

Ramaekers et al. (2011) measured the residual effects of single and repeated doses of esmirtazapine 1.5 and 4.5 mg on real-life driving performance in 32 healthy volunteers in a double-blind, placebo-controlled study. Treatment with single doses of zopiclone 7.5 mg was included as an active control. Treatments were administered in the evening. Driving performance was assessed in the morning, 11 hours after drug intake. Single-dose zopiclone 7.5 mg increased SDLP.

Verster et al. (2011) reviewed eight studies utilising the standardised on-the-road driving test that consistently showed that in the morning following bedtime administration zopiclone (7.5 mg) significantly impaired driving performance. Meta-analyses showed no significant differences in driving performance after zopiclone (7.5 mg) between adult and elderly healthy volunteers. The combined effect size for healthy volunteers was 0.782 (95 % CI 0.620–0.944). Relative to placebo, an average increment in SDLP of 3.0 cm was observed following treatment with zopiclone (7.5 mg). This deviation was higher than the increment in SDLP reported for drivers with a BAC of 0.5 g/l (+2.4 cm). Results from driving simulators and psychometric tests are consistent with the on-road driving test results. In a literature review (Verster and Roth, 2012), significant sex differences (higher SDLP in women) in driving performance the morning following bedtime administration of flurazepam (30 mg) and after middle-of-the-night administration of zolpidem (10 mg) were observed. No significant sex differences were found for ramelteon (8 mg), lormetazepam (1 and 2 mg), zaleplon (10 and 20 mg) or zopiclone (7.5 mg).

Medium-acting benzodiazepines

Alprazolam

Mills et al. (2001) studied the effects of stimulants and sedatives on performance on single-target and divided attention tasks in different parts of the visual field in fully rested participants: alprazolam (0.5 mg) clearly impaired performance whereas stimulants (dextroamphetamine 10 mg) enhanced performance and induced tunnel vision.

Verster et al. (2002b) examined the effects of alprazolam (1 mg) on driving ability, memory and psychomotor performance. One hour after intake, the volunteers took a standardised driving test during which SDLP and standard deviation of speed were measured. In addition, 2.5 hours after administration a laboratory test battery, including a memory scanning test, tracking test and divided attention test, was carried out. Serious driving impairment was encountered, which was also confirmed by subjective assessments. Moreover, alprazolam 1 mg seriously impaired performance on the laboratory test.

In a review of alprazolam studies, Verster and Volkerts (2004a) summarised the effects of the drug on memory and driving ability. For memory functioning, a clear dose–impairment correlation was seen.

Leufkens et al. (2007) studied the effects of 1 mg alprazolam extended release and 1 mg alprazolam immediate release. A standardised driving test was performed 4 hours after dosing, cognitive and psychomotor tests were performed 2.5 and 5.5 hours after dosing and memory function was assessed 1 hour after administration. Severe impairment of driving performance was noted. Impairment with the extended-release formulation was only half of that observed with the immediate-release formulation.

Previously, Bourin et al. (1998) showed that low doses of lorazepam or alprazolam produced significant improvement in cognitive and psychomotor functions in healthy volunteers. A study by Bentué-Ferrer et al. (2001) in animals found a behavioural stimulatory effect with alprazolam (0.005 mg/kg) but not with lorazepam, which the authors supposed was because of the extracellular rise of dopamine in the striatum.

Snyder et al. (2005) found that alprazolam 0.5 mg reduced the speed of attentional performance. With a

dose of 1 mg, impairments in psychomotor functions were observed in addition to impairments in working memory and learning.

In one of the DRUID experimental studies (Schulze et al., 2012), zopiclone (7.5 mg) and alprazolam (0.5 mg) produced significant driving impairment in patients as well as in healthy control subjects. Zolpidem (10 mg) produced significant driving impairment in elderly subjects. Chronic users did not experience subjectively any sedative effects of zopiclone and alprazolam, whereas infrequent users and healthy users reported feelings of reduced alertness and sleep. This lack of awareness of (residual) sedative effects of zopiclone and alprazolam may lead patients who suffer from insomnia and anxiety to believe that car driving is safe during treatment with these drugs.

Lorazepam

In a study of the subchronic use of lorazepam or ritanserin, Van Laar et al. (2001) evaluated subjects' driving performance, slow-wave sleep and daytime sleepiness. Lorazepam 1.5 mg, ritanserin 5 mg or placebo was given twice daily for 7 days. Tests included EEG, sleep latency test, driving test (SDLP) and subjective assessments. With lorazepam, marked impairment on the driving test and a reduction in daytime sleepiness were observed.

Matthews et al. (2002) studied the effects on memory and behavioural learning of a single dose of lorazepam 2.5 mg. Marked deficits in delayed free recall, perceptual priming and written word fluency were recorded, with preservation of digit span. The results suggest an impairment of the ability to learn behavioural strategies.

The effects of lorazepam on total and partial retrieval of recently learned material and feeling-of-knowing rating were studied by Izaute and Bacon (2006). When studying four-letter nonsense letter strings, the subjects taking lorazepam (0.038 mg/kg) showed an impairment of episodic short-term memory. The drug also had an effect on the feeling-of-knowing estimates, but not on their predictive accuracy.

Clarkson et al. (2004) reviewed driving ability in individuals suspected of driving under the influence of drugs and in whom a blood sample subsequently tested positive for lorazepam. Among those in whom lorazepam alone was detected, significant psychomotor disability that was independent of the blood concentration (range 0.01–0.13 mg/l) of lorazepam was found.

A study by Soo-ampon et al. (2004) found that effects on recall memory of lorazepam 2 mg alone, alcohol 0.6 g/l alone or the two combined were significantly dependent on word frequency. Low-frequency words were more sensitive to memory impairment by lorazepam or alcohol than high-frequency ones. However, subjects' more accurate recall of the high-frequency words was eliminated when both lorazepam and alcohol were consumed.

Lormetazepam

Iudice et al. (2002) assessed the effects of lormetazepam (1 mg) on daytime vigilance, psychomotor performance and simulated driving. For 3 days, subjects received lormetazepam or placebo at night, and tests were conducted on the morning following the last administration. Subjects' results on neuropsychological tests, visual reaction times, sleep latency and driving ability showed no deterioration following placebo or active medication when compared with baseline performance.

Psychomotor performance in young adults given a single dose of lormetazepam or placebo was assessed using visual SRT and visual CRT, measured before and after dosing (Fabbrini et al., 2005). Lormetazepam did not affect psychomotor performance compared with placebo.

Temazepam

Tiplady et al. (2003) tested the difference between alcohol (0.8–1.0 g/l) and temazepam (20–30 mg) on generating errors in performance tests. Alcohol generated more error-prone behaviour with less effect on psychomotor speed. Temazepam had no significant effect on accuracy but slowed performance. Information-processing capacity and long-term memory formation were reduced in a similar way with both alcohol and temazepam 30 mg.

Morin et al. (2003) reported few adverse effects of temazepam (7.5–30 mg) in older adults. Those that were observed were in the areas of affective/behavioural/cognitive function, neurosensory function and neuro-automatic function. Tolerance to these effects developed over time.

Long-acting benzodiazepines

The behavioural and cognitive effects of flunitrazepam and clonazepam were examined by Dowd et al. (2002). Flunitrazepam (2 mg) affected memory and attention

4 hours after intake, while clonazepam (3 mg) affected memory and attention for 6 hours and reduced psychomotor performance 2 hours after intake.

Bramness et al. (2006) investigated the relationship between impairment and flunitrazepam concentrations in the blood of drivers suspected of impairment. The impaired drivers had higher flunitrazepam concentrations than the drivers who were not impaired. Paradoxical reactions were observed, but were not related to the flunitrazepam level.

A study by Rich et al. (2006) evaluated the effect of diazepam 0.19 mg/kg on retrospective and prospective memory by testing free recall of unrelated word lists and instructing the participants to request the return of a belonging that they had given to the experimenter at the start of the session. Diazepam impaired performance on all measures.

Boucart et al. (2007) investigated attentional impairments in the temporal domain in conditions simulating driving, in which observers had to read the name of a city and then detect a vehicle appearing to the left or right of the fixation point at short but variable temporal intervals. Diazepam, at therapeutic dosage, impaired shifting of attention when participants were asked to process two events occurring in rapid succession.

Between-group comparisons

Bocca et al. (1999) studied the residual effects of zolpidem 10 mg, zopiclone 7.5 mg, flunitrazepam 1 mg or placebo on driving performance. Doses were given at 11.00 p.m. Zopiclone and flunitrazepam had residual effects during the first part of the morning, while zolpidem was free of any effect. In addition, flunitrazepam and zopiclone affected eye movements (saccadic latency) adversely.

Vignola et al. (2000) compared people with insomnia not using medications, people with insomnia using medication (lorazepam, flurazepam, nitrazepam or temazepam) and good sleepers on neuropsychological tests for memory, attention/concentration and psychomotor function. Both groups with insomnia performed worse than good sleepers. Subjects with insomnia who were not taking medications had lower performance expectations and rated their own performance more negatively.

Partinen et al. (2003) investigated the effects of an after-midnight intake of zolpidem (10 mg), temazepam (20 mg) or placebo on driving ability in women with non-organic insomnia. The subjects underwent a driving simulator test 5.5 hours after intake. No major differences in psychomotor performances were observed between those taking either zolpidem or temazepam and those given placebo, leading the authors to conclude that there was an absence of significant residual effects. However, differences in susceptibility to the drugs were seen among the subjects.

The effects of zolpidem 5 mg, zopiclone 3.75 mg or lormetazepam 1 mg in elderly people were investigated by Allain et al. (2003) using LMT, CTT, SRT and a Sternberg test. SRT and CTT results were unaffected by the three drugs, whereas lormetazepam led to an impairment of performance on the LMT.

Vermeeren (2004) reviewed the effects of 11 hypnotics. Zaleplon 10 or 20 mg, zolpidem 10 mg, temazepam 20 mg (soft gel capsules), lormetazepam 1 mg capsules and triazolam 0.125 mg were unlikely to have any residual effects the morning after administration. Tolerance to these impairment effects upon continued administration seems to occur, but it may be only partial and dependent upon dose and duration of administration.

The acute pharmacological effects of temazepam (15 or 30 mg), diphenhydramine (50 or 75 mg) and the herbal supplement valerian (400 or 800 mg) were examined by Glass et al. (2003). Psychomotor effects were assessed with the DSST and manual tracking. Valerian had no effect, while temazepam 30 mg produced the most psychomotor impairment. Diphenhydramine 75 mg and temazepam 15 mg produced similar effects on motor performance, and no psychomotor impairment was detected with diphenhydramine 50 mg.

Staner et al. (2005) evaluated the effects of zolpidem (10 mg), zopiclone (7.5 mg) or lormetazepam (1 mg) on EEG and a driving simulation test 9–11 hours after administration. Zopiclone increased the number of collisions and lormetazepam increased the deviation from speed limit and deviation from absolute speed, while zolpidem had no effects. EEG recordings showed typical benzodiazepine-induced alterations.

The modification of visual information processing was studied by Berthelon et al. (2003). A night-time dose of zolpidem (10 mg), zopiclone (7.5 mg) or flunitrazepam (1 mg) was given and the effects on collision anticipation capacities were investigated the next morning. Only flunitrazepam caused subjects to incorrectly focus their attention during the simulation.

A study by Paul et al. (2003) comparing melatonin 6 mg slow release, zaleplon 10 mg, zopiclone 7.5 mg and temazepam 15 mg showed that all the substances except melatonin caused detrimental effects on psychomotor performances tested using the SRT, logical reasoning task, serial subtraction task and multitask. The time to normal recovery on the SRT following zaleplon, zopiclone and temazepam was 3.25 hours, 6.25 hours and 5.25 hours, respectively.

Berthelon et al. (2008) compared the residual effects of zopiclone (7.5 mg), zolpidem (10 mg) and flunitrazepam (1 mg) with those of a placebo on the capacity of subjects to estimate their own speed of movement and to anticipate a situation of collision with another vehicle parked along their trajectory. They found that own speed perception and time to collision estimation were not affected by the residual effects of the hypnotic drugs studied. Thus, the behavioural impairment observed in previous studies results from the alteration of other functions that are used when driving a vehicle.

Meskali et al. (2009) administered zopiclone (7.5 mg), zolpidem (10 mg) and flunitrazepam (1 mg; used as positive control) to 16 healthy subjects aged 55–65 years at each subject's home at 11.00 p.m. The next morning, the subjects had to drive in a simulated urban environment in which accident scenarios were introduced. Hypnotics did not significantly increase the number of collisions. However, those subjects given zopiclone and flunitrazepam drove at significantly higher speeds; moreover, zolpidem and zopiclone induced modifications of the lateral position of the car on the road. Verster et al. (2007) stated that zolpidem is a safe alternative to benzodiazepine hypnotics and zopiclone, both of which cause significant driving impairment the morning after bedtime administration if patients take the medication just before a full 8 hours of uninterrupted sleep.

Gaboxadol, a selective extrasynaptic $GABA_A$ receptor agonist previously in development for the treatment of insomnia, has a short half-life (1.5–2 hours) and is expected to be free from residual effects the next morning. Leufkens et al. (2009) assessed the residual effects of evening and middle-of-the-night administration of 15 mg of gaboxadol on cognitive, psychomotor and driving performance in 25 healthy volunteers. On each treatment night, subjects ingested one capsule at 11.00 p.m. and one at 4.00 a.m. Treatments were placebo at both times, 15 mg gaboxadol or 7.5 mg zopiclone followed by placebo, and placebo followed by 15 mg gaboxadol or 10 mg zolpidem. Effects on cognition and psychomotor performance were assessed between 7.30 a.m. and 8.30 a.m. and on driving (SDLP) between 9.00 and 10.00 a.m. Driving was almost significantly ($p < 0.07$) impaired after evening administration of gaboxadol. The effects of all other active treatments on driving were significant. Evening administration of gaboxadol had minor effects on divided attention only, whereas middle-of-the-night administration impaired performance significantly in all tests except memory. Zolpidem and zopiclone impaired performance significantly in every test except tracking after zopiclone.

Several cases of sleep driving, a variant of sleepwalking, after use of zolpidem have been described (Hoque and Chesson 2009; Poceta, 2011; Pressman, 2011). All subjects reported amnesia for 3–5 hours. In some cases, the episodes began during daytime wakefulness because of accidental or purposeful ingestion of zolpidem and are considered automatisms. Other cases began after ingestion of zolpidem at the time of going to bed and are considered parasomnias.

An expert panel in Norway (Vindenes et al., 2012) proposed cut-off values for different benzodiazepines in blood, corresponding to alcohol concentrations of 0.2, 0.5 and 1.2 g/l (Table 4).

TABLE 4

Impairment limits and limits for graded sanctions proposed in Norway for different benzodiazepines and Z-hypnotics (Vindenes et al., 2012)

	Impairment limit (ng/ml)	Limit for graded sanctions corresponding to BAC 0.5 g/l (ng/ml)	Limit for graded sanctions corresponding to BAC 1.2 g/l (ng/ml)
Alprazolam	3	6	15
Clonazepam	1.3	3	8
Diazepam	57	143	342
Flunitrazepam	1.6	3	8
Nitrazepam	17	42	98
Oxazepam	172	430	860
Phenazepam	1.8	5	10
Zolpidem	37	77	184
Zopiclone	12	23	58

TABLE 5

Results of the large meta-analysis of the experimental studies in the DRUID project (part 1)

	Oxazepam	Lorazepam	Bromazepam	Alprazolam	Diazepam	Chlordiazepoxide	Clobazam	Buspirone
Number of studies/ number of effects	26/377	68/1 244	9/202	21/354	103/2 104	9/101	16/287	16/341
Dose (mg)	30	2.5	12	1	20	60	20	20
Maximum percentage of impaired results	52	77	45	74	74	< 30	< 15	<10
Time (h) of maximum impairment	2.25	3.25	2	2.0	1.25	–	3	2–4
Duration (h)	9.0	19.75	–	14	6.25	–	0	0
Equivalent BAC (g/l)	> 0.8	> 0.8	> 0.8	> 0.8	> 0.8	0.3–0.5	< 0.3	< 0.3
Degree of impairment (1)	170	571	–	369	171	–	0	0
Concentration equivalent to BAC 0.5 g/l	330	9	–	9	320	–	–	–

(1) The time that a subject who has taken the drug is impaired by more than 15 % (equivalent to a BAC of 0.3 g/l) in arbitrary units.
NB: –, too few data to calculate the number. If multiple doses were given, only the highest is given in this table. Abbreviation: BAC, blood alcohol concentration.

TABLE 6

Results of the large meta-analysis of the experimental studies in the DRUID project (part 2)

	Triazolam	Lormetazepam	Temazepam	Flurazepam	Flunitrazepam	Zopiclone	Zoplidem	Zaleplon
Number of studies/ number of effects	46/1 305	13/161	30/695	22/203	29/491	21/331	31/857	12/350
Dose (mg)	0.5	2.0	20	30	2	7.5	20	10
Maximum percentage of impaired results	71	27	30	70–75	92	58	64	37
Time (h) of maximum impairment	1.75	0.5	2	2–11	2.25	2.25	1.5	0.75
Duration (h)	10	4.25	0	> 24	> 15	11.5	17	3.5
Equivalent BAC (g/l)	> 0.8	0.3–0.5	0.5	> 0.8	> 0.8	> 0.8	> 0.8	0.5–0.8
Degree of impairment (1)	247	22	0	–	461	240	214	40
Concentration equivalent to BAC 0.5 g/l	1.6	9.2	450	–	5.4	26	71	

(1) The time that a subject who has taken the drug is impaired by more than 15 % (equivalent to a BAC of 0.3 g/l) in arbitrary units.
NB: –, too few data to calculate the number. If multiple doses were given, only the highest is given in this table. Abbreviation: BAC, blood alcohol concentration.

Meta-analysis of experimental studies

Berghaus et al. (2010) performed a large meta-analysis of the experimental studies in the DRUID project. A summary of the results is given in Tables 5 and 6.

Chronic effects

Vermeeren and Coenen (2011) concluded that studies of the long-term use of benzodiazepine hypnotics suggest that effects on daytime performance may diminish over time owing to tolerance. However, there are also studies showing that performance may improve after discontinuation of chronic benzodiazepine use, which suggests that tolerance may not be complete.

Combination with other substances

Few studies exist on the combined effects of alcohol and benzodiazepines. One study by Simpson and Rush (2002) showed that triazolam (0.125 or 0.250 mg) and temazepam (15 or 30 mg) each produced some impairment, whereas alcohol alone (0.5 g/l) did not. Triazolam–alcohol and temazepam–alcohol combinations resulted in clear impairment, even with low amounts of alcohol.

Maxwell et al. (2010) used data from the Fatality Analysis Reporting System (1993–2006) on drivers aged 20 or older who were tested for both alcohol and drugs. Using a case–control design, they compared drivers who had at least one unsafe driver action (e.g. weaving) recorded in relation to the crash (cases) with drivers who did not (controls). Drivers who tested positive for intermediate- and long-acting benzodiazepines in combination with alcohol had significantly greater odds of an unsafe driver action than those under the influence of alcohol alone, up to BACs of 0.8 and 0.5 g/l, respectively. The odds of an unsafe driver action with short-acting benzodiazepines combined with alcohol were no different than for alcohol alone.

Concentration–effect relationship

Smink et al. (2008a) studied the relationship between the blood concentration of benzodiazepines and performance in field sobriety tests in 171 retrospective cases. Observations of behaviour (n = 137; $p < 0.01$), walking (n = 109; $p < 0.01$), walking after turn (n = 89; $p = 0.02$) and Romberg's test (n = 88; $p < 0.05$) were significantly related to the benzodiazepine concentration. There was no significant relation between benzodiazepine concentration and effect on pupil size, nystagmus or orientation.

Verster and Roth (2013) identified 11 studies that employed the on-the-road driving test to examine driving performance after administration of benzodiazepine receptor agonists and also measured blood drug concentrations after the on-the-road driving test was performed. Although group mean average ΔSDLP (difference in SDLP) and blood drug concentration are sometimes correlated, individual differences in blood concentrations of benzodiazepine receptor agonists correlate poorly with driving impairment. From the currently available data, it must be concluded that there are no significant relationships between individual blood drug concentration and ΔSDLP.

Risks

Bramness et al. (2002) examined the relationship between benzodiazepine concentration and impairment in apprehended drivers. Substances tested for were diazepam, oxazepam, flunitrazepam, nitrazepam, alprazolam, triazolam and clonazepam. A higher blood concentration of diazepam, oxazepam and flunitrazepam was found in the impaired subjects than in the subjects who were not impaired. There was a clear concentration-related effect of benzodiazepines on performance.

Accident risk

A case–control analysis in Canada found that drivers testing positive for benzodiazepines had a higher risk of being involved in a traffic accident (OR 4.2; 95 % CI 2.7–6.3) (Dussault et al., 2002). Testing positive for benzodiazepines alone, a combination of benzodiazepines and cannabis or a combination of benzodiazepines, cannabis and alcohol was associated with an increased accident risk of 2.5 (OR; 95 % CI 1.4–4.3), 21.3 (OR; 95 % CI 5.3–86.0) and 63.9 (OR; 95 % CI 6.6–618.0), respectively. A combination of benzodiazepines and alcohol (BAC > 0.8 g/l) was associated with an infinitely increased risk of being involved in a traffic accident, but this is probably because of the small number of drivers testing positive for this combination. A comparison of the prevalence of alcohol, drugs and medicines among 900 injured drivers and 900 control subjects in France found that benzodiazepines alone are associated with an increased accident risk of 1.7 (OR; 95 % CI 1.2–2.4) (Mura et al., 2003). The Immortal study in the Netherlands and in Norway found that benzodiazepines alone generate an increased accident risk of 3.0 (RR; 95 % CI 1.3–6.8) and 20.6 (OR; 95 % CI 2.1–201.8), respectively (Assum et al., 2005).

One pharmacoepidemiological study investigated the relationship between responsibility for a traffic accident and benzodiazepine use in the elderly (McGwin et al., 2000). The results showed that use of benzodiazepines was not associated with an increased risk of responsibility for an accident. However, pharmacoepidemiological studies published before 1999 do report that benzodiazepine use is associated with an increased accident risk (Barbone et al., 1998; Hemmelgarn et al., 1997) and an increased injury risk (Neutel, 1995, 1998).

In a registry-based cohort study, Engeland et al. (2007), using the SIR, compared the incidence of accidents as a function of exposed person-time with the incidence in the unexposed person-time. The risk was markedly increased in users of benzodiazepine tranquillisers (2.9; 95 % CI 2.5–3.5) and benzodiazepine hypnotics (3.3; 95 % CI 2.1–4.7).

Hébert et al. (2007) compared the results of an unmatched case–control study with those of a case-crossover study using the same prescription claims database to determine whether current use of benzodiazepines increases the risk of motor vehicle crashes. The case–control approach identified 5 579 cases (drivers involved in crash resulting in injury) and 12 911 controls (a 6.2 % subsample of all 224 734 eligible drivers) between the years 1990 and 1993 in the

province of Quebec, Canada. An increased rate of injurious motor vehicle crashes was associated with current use of long-acting benzodiazepines (OR 1.45; 95 % CI 1.12–1.88). The case-crossover approach applied to all cases did not find any association (OR 0.99; 95 % CI 0.83–1.19). However, when cases were restricted to subjects with four or fewer prescriptions filled in the previous year, corresponding more to transient exposures, the OR was elevated (OR 1.53; 95 % CI 1.08–2.16). A case–control study in southern Taiwan (Hou et al., 2012) from January 2009 to December 2009 and involving 254 injured patients and 254 control drivers found that the risk of hospitalisations as a result of motor vehicle crashes was increased in those taking benzodiazepines (OR 3.41; 95 % CI 1.76–6.70) and those taking alcohol (BAC ≥ 0.8 g/l) (OR 3.50; 95 % CI 1.81–6.85). Among participants taking combinations of benzodiazepines and alcohol, the OR increased to 5.12 (95 % CI 1.77–15.91).

Based on the DRUID results in Belgium (Kuypers et al., 2012), only crude ORs for the risk of crash with injuries associated with sedative and hypnotic drugs could be calculated: 1.34 (95 % CI 0.53–3.40) for benzodiazepines and 6.45 (95 % CI 1.63–25.52) for Z-hypnotics. For the combination of alcohol and sedatives, the adjusted OR was 67.19 (95 % CI 23.91–188.84), and for the combination of different sedatives the adjusted OR was 13.70 (95 % CI 2.95–63.66).

In the DRUID case–control study (Hels et al., 2011), the relative risk of serious injury when driving under the influence of benzodiazepines and Z-hypnotics was estimated to be increased to a middling extent (2–10). The adjusted OR, based on data for all countries, was 1.99 (95 % CI 1.36–2.91) for serious injury and 5.40 (95 % CI 3.90–7.46) for death.

Meuleners et al. (2011), in a retrospective, population-based, case-crossover study in Western Australia between 2002 and 2008, determined the association between psychoactive medications and crash risk in 616 drivers aged 60 and older. The risk of being involved in a crash resulting in hospitalisation was higher for older drivers when they were prescribed benzodiazepines (OR 5.3; 95 % CI 3.6–7.8). Crash risk was significantly higher in both men (OR 6.2; 95 % CI 3.2–12.2) and women prescribed benzodiazepines (OR 4.9; 95 % CI 3.1–7.8). Subgroup analyses further suggested that drivers who were prescribed benzodiazepines were at greater crash risk whether they had (OR 4.0; 95 % CI 2.9–8.1) or did not have (OR 6.0; 95 % CI 3.8–9.5) a chronic condition.

Yang et al. (2011) determined whether the use of zolpidem 1 day previously is associated with an increased risk of an MVA. Using a case-crossover design, they selected the day before an MVA as the case period for each subject, and days 91, 182 and 273 before the case period as three retrospective control periods. The adjusted OR for involvement in an MVA after taking one defined daily dose of zolpidem was 1.74 (95 % CI 1.25–2.43).

Gustavsen et al. (2008) investigated whether filling a prescription for zopiclone or zolpidem was associated with an increased risk of road traffic accidents at a national population level in Norway. Nitrazepam and flunitrazepam were used as comparator drugs. The first week after the hypnotics had been dispensed was considered the exposure period. SIRs were calculated by comparing the incidence of accidents in the exposed person-time with the incidence of accidents in the unexposed person-time. The SIRs for all ages and both sexes combined were 2.3 (95 % CI 2.0–2.7), 2.7 (95 % CI 1.8–3.9) and 4.0 (95 % CI 2.4–6.4) for Z-hypnotics (zopiclone + zolpidem), nitrazepam and flunitrazepam, respectively. The highest SIRs were found among the youngest users for all hypnotics.

In a French registry-based study on the risk of road traffic crashes in people who were prescribed medicines, Orriols et al. (2010) found an OR of 1.27 (95 % CI 1.15–1.405) for psycholeptics (N05 in the ATC classification; this class includes antipsychotics and anxiolytics).

Ravera et al. (2011) examined the association between the use of commonly prescribed psychotropic medications and road traffic accident risk in the Netherlands in 2000 and 2007. A significant association was found between traffic accident risk and exposure to anxiolytics (OR 1.54; 95 % CI 1.11–2.15). A statistically significant increased risk was also seen in chronic anxiolytic users, females and young users (18–29 years old) and users of hypnotics with an intermediate half-life.

Responsibility analyses

In Australia, a study on alcohol and drug use among 3 398 fatally injured drivers indicated that drivers testing positive for benzodiazepines did not have an increased risk of responsibility for the accident (OR 1.3; 95 % CI 0.5–3.3) (Drummer et al., 2004). Another study in Australia assessed the relationship between drug prevalence, drug concentration and driver responsibility among 2 500 injured drivers (Longo et al., 2000b). This study found a significant relationship between use of benzodiazepines alone and responsibility (OR 2.0; 95 % CI 1.1–3.9) as well as between benzodiazepine

concentration and responsibility. The risk of responsibility for an accident was higher for a combination of alcohol and benzodiazepines (OR 13.4; 95 % CI 1.8–101.0) than for benzodiazepines alone or alcohol alone (OR 8.0; 95 % CI 5.3–12.2). There was an infinite risk associated with the use of a combination of benzodiazepines and cannabis because all drivers testing positive for this combination were judged responsible. A responsibility analysis in Canada of 482 fatally injured drivers found that drivers testing positive for benzodiazepines, or for benzodiazepines alone, had no higher risk of responsibility for an accident (OR 5.8, 95 % CI 0.7–44.4; OR 3.6, 95 % CI 0.5–28.2, respectively) (Dussault et al., 2002). The combination of benzodiazepines with either alcohol (BAC > 0.8 g/l) or cannabis or with both substances was associated with an infinite accident risk, probably because all drivers testing positive for these combinations were judged responsible.

Dubois et al. (2008), in a case–control study of drivers aged 20 and over involved in fatal crashes in the United States from 1993 to 2006, examined the impact of benzodiazepines on crash responsibility according to drug half-life and driver age. Drivers (all with BAC = 0) were classified as having no benzodiazepines detected or testing positive for benzodiazepines with a short, intermediate or long half-life. Cases were drivers deemed to have performed at least one potentially unsafe driving action in relation to the crash (e.g. speeding), a proxy measure for crash responsibility; controls were drivers who took no unsafe driving actions. The ORs of taking any unsafe driving action according to exposure to benzodiazepines of varying half-life were calculated, with adjustment for age, sex, other medication usage and prior driving record. The odds of an unsafe driving action were increased by taking benzodiazepines with an intermediate or long half-life in drivers aged 25 (intermediate half-life: OR 1.59, 95 % CI 1.08–2.33; long half-life: OR 1.68, 95 % CI 1.34–2.12) to 55 (intermediate half-life: OR 1.50, 95 % CI 1.09–2.06; long half-life: OR 1.33, 95 % CI 1.12–1.57). The odds of drivers taking short half-life benzodiazepines performing an unsafe driving action were not increased compared with drivers not using benzodiazepines.

Orriols et al. (2011) investigated the association between the use of benzodiazepine or benzodiazepine-like hypnotics and the risk of road traffic accidents by matching data from three French national databases: the healthcare insurance database, police reports and the police database of injury-related traffic accidents. A total of 72 685 drivers involved in injury-related road traffic accidents in France, from 2005 to 2008, were included in the study. The risk of responsibility for a traffic accident was higher in users of benzodiazepine hypnotics (OR 1.39; 95 % CI 1.08–1.79) and particularly in the drivers to whom a dosage of more than one tablet of 10 mg zolpidem a day had been dispensed during the 5 months before the crash (OR 2.46; 95 % CI 1.70–3.56). No association was found between the use of zopiclone and risk of traffic accidents.

Meta-analysis

A meta-analysis was performed on the data from the case–control studies in France, the Netherlands and Norway (Assum et al., 2005; Mura et al., 2003). The results indicate that drivers who test positive for benzodiazepines alone are at an increased risk of being involved in an accident, as shown by an RR of 2.3 (95 % CI 2.0–2.7) and an OR of 3.4 (95 % CI 2.5–4.4). A meta-analysis was also performed on the data from the two responsibility analyses in Australia (Drummer et al., 2004; Longo et al., 2000b). The combined data showed an increasing but non-significant accident risk (OR 1.5, 95 % CI 0.9–2.4; RR 1.1, 95 % CI 1.0–1.3).

Dassanayake et al. (2011) performed a systematic review and meta-analysis. Twenty-one epidemiological studies (13 case–control and eight cohort studies) ascertained by blood or urine analysis or prescription records were included. Sixty-nine experimental studies fulfilled the inclusion criteria by testing actual or simulated driving performance after administering a single dose or multiple doses. Two meta-analyses showed that benzodiazepines are associated with a 60 % (for case–control studies: pooled OR 1.59; 95 % CI 1.10–2.31) to 80 % (for cohort studies: pooled incidence rate ratio 1.81; 95 % CI 1.35–2.43) increase in the risk of traffic accidents and a 40 % (pooled OR 1.41; 95 % CI 1.03–1.94) increase in 'accident responsibility'. Co-ingestion of benzodiazepines and alcohol was associated with a 7.7-fold increase in the accident risk (pooled OR 7.69; 95 % CI 4.33–13.65). Subgroup analysis of case–control studies showed a lower benzodiazepine-associated accident risk in elderly (> 65 years of age) drivers (pooled OR 1.13; 95 % CI 0.97–1.31) than in drivers under the age of 65 (pooled OR 2.21; 95 % CI 1.31–3.73). Anxiolytics, taken in single or multiple doses during the daytime, impaired driving performance independent of their half-lives. Regarding hypnotics, converging evidence from experimental and epidemiological studies indicates that diazepam, flurazepam, flunitrazepam, nitrazepam and the short half-life non-benzodiazepine hypnotic zopiclone significantly impair driving, at least during the first 2–4 weeks of treatment.

In their meta-analysis, Rapoport et al. (2009) included 16 experimental studies using driving simulators and

on-road tests and 11 epidemiological studies of a case–control or cohort design. Data were extracted by blinded raters and pooled using random-effects models. They excluded studies without control groups or without measures of driving or collisions. Associations between motor vehicle collisions and benzodiazepine use were found among six case–control studies (OR 1.61; 95 % CI 1.21–2.13) and three cohort studies (OR 1.60; 95 % CI 1.29–1.97). Only 10 of 97 experimental driving variables could be pooled for analysis. While no consistent findings were observed in studies using driving simulators, increased SDLP was found on on-road driving tests (standardised mean difference 0.80; 95 % CI 0.35–1.25).

In their systematic review of 66 epidemiological studies that investigated the association between benzodiazepine use and traffic accidents, including related outcomes such as culpability and injury or accident severity, Smink et al. (2010) found that the greatest accident risk is associated with the use of long half-life benzodiazepines, increasing dosage and the first few weeks of use of benzodiazepines. Clear evidence of increased culpability associated with benzodiazepine use is scarce.

In their meta-analysis of 10 experimental studies, Verster et al. (2006) found that the recommended dose of various benzodiazepine hypnotics resulted in significant driving impairment the morning after bedtime administration, i.e. 10–11 hours after dosing [effect size (ES) 0.42; 95 % CI 0.14–0.71]. Twice the recommended dose impaired driving both in the morning (ES 0.68; 95 % CI 0.39–0.97) and in the afternoon, i.e. 16–17 hours after dosing (ES 0.57; 95 % CI 0.26–0.88). Zopiclone 7.5 mg also impaired driving in the morning (ES 0.89; 95 % CI 0.54–1.23). Zaleplon (10 and 20 mg) and zolpidem (10 mg) did not affect driving performance the morning after dosing. Following middle-of-the-night administration, significantly impaired driving performance was found for zopiclone 7.5 mg (ES 1.51, 95 % CI 0.85–2.17), zolpidem 10 mg (ES 0.66; 95 % CI 0.13–1.19) and zolpidem 20 mg (ES 1.16; CI 0.60–1.72). Zaleplon (10 and 20 mg) did not affect driving performance.

In the meta-analysis of 66 publications by Elvik (2013), the best estimate of the relative risk of accident involvement with benzodiazepines, adjusted for publication bias, was 2.30 (95 % CI 1.59–3.32) for fatal accidents, 1.07 (95 % CI 0.98–1.16) for injury accidents and 1.35 (95 % CI 1.04–1.76) for crashes with property damage. For zopiclone, the ORs were 2.60 (95 % CI 0.89–7.56) for fatal accidents, 1.42 (95 % CI 0.87–2.31) for injury accidents and 4.00 (95 % CI 1.31–12.21) for crashes with property damage.

Conclusion

Acute effects: Benzodiazepines and Z-hypnotics are a group of substances that cause impairment ranging from severe effects to almost no effect. Of the short-acting benzodiazepines and benzodiazepine-like drugs, zaleplon showed few impairing effects (though some for 20 mg doses), whereas zolpidem and zopiclone, and to some extent triazolam, did produce impairment. Among the intermediate-acting benzodiazepines, alprazolam and lorazepam caused marked impairment, and lormetazepam and temazepam less so. The limited studies using long-acting benzodiazepines showed impairment for flunitrazepam, clonazepam and diazepam. Significant sex differences (higher SDLP in women) in driving performance were observed the morning following administration of flurazepam and zolpidem, but not for other benzodiazepines. Several cases of sleep driving, a variant of sleepwalking, after zolpidem use have been described.

Duration of effects: A few benzodiazepines should generally be regarded as unlikely to have a residual effect the morning after night-time use: zaleplon 10 mg, lormetazepam 1 mg and temazepam 20 mg (immediate-release capsules). Zolpidem 10 mg produced no effect 8.25 hours after administration, while zaleplon 20 mg showed conflicting results. Zolpidem is a safe alternative to benzodiazepine hypnotics and zopiclone, both of which result in significant driving impairment the morning following bedtime administration if patients take the medication just prior to a full 8 hours of uninterrupted sleep. Temazepam 20 mg was found to be unlikely to impair driving 10 hours or more after bedtime administration in healthy elderly drivers aged 75 years or younger. Zopiclone 7.5 mg moderately impaired driving in the elderly at least until 11 hours after administration. The time of maximum impairment varies between 1.2 and 11 hours and the maximum duration of impairment can be longer than 24 hours, depending on the benzodiazepine.

Combinations: When combined with alcohol, consumption of temazepam, lorazepam and triazolam caused clear impairment. The risk of being involved in or responsible for an accident increases when another psychoactive substance (usually alcohol and/or cannabis) is taken in combination with a benzodiazepine.

Chronic use: With chronic and subchronic use, tolerance might develop, partially or completely, to the impairing effects. Studies on long-term use of benzodiazepine hypnotics suggest that effects on daytime performance may diminish over time as a result of tolerance. However, there are also studies showing that performance may

improve after discontinuation of chronic benzodiazepine use, which suggests that tolerance may not be complete.

Threshold concentration: From the data collected, there is a correlation between plasma levels and degree of impairment (less obvious for lorazepam), be it on memory or on psychomotor performance. However, individual susceptibility and tolerance must still be taken into account. An expert panel in Norway proposed impairment limits for different benzodiazepines in blood ranging from 1.3 ng/ml for clonazepam to 172 ng/ml for oxazepam.

Accident risk: Epidemiological studies indicate that drivers have an increased risk of being involved in a traffic accident after having taken a benzodiazepine, although no distinction was made between the different kinds of benzodiazepines. The results of responsibility analyses are contradictory. Only one study (out of three) found that drivers testing positive for benzodiazepines are at an increased risk of responsibility for an accident, and that the risk rises with increased concentrations of benzodiazepines. Meta-analyses show that the relative risk of crashes is approximately 1.6–1.8 for benzodiazepines. In combination with alcohol, the relative risk increases to approximately 8.

Antihistamines

Antihistamines are drugs used to treat allergic reactions. They work by blocking the peripheral and central effects of histamines by binding to histamine receptors. The known histamine receptors include H_1, H_2, H_3 and H_4 receptors. Histamines are released as the result of an allergic response to different types of allergens (e.g. certain drugs, venoms, peptides), and can lead to vasodilation, increased permeability of blood vessels and contraction of smooth muscles (including bronchoconstriction). Treatment with H_1 antihistamines can rapidly resolve these symptoms but can also cause adverse effects. Depending on the distribution of the drug in the body, the adverse effects can include sedation, effects on the digestive tract and anticholinergic effects. The antihistamines discussed here are largely H_1-receptor antagonists, although some show affinity for other histamine receptors (sometimes acting as agonists rather than antagonists) or muscarinergic, adrenergic or serotoninergic receptors as well as for cardiac ion channels (calcium and potassium) — hence the broad range of adverse effects. The H_1 receptor is found in neurons, smooth muscle cells, epithelial and endothelial cells and white blood cells. The H_1-receptor antagonists are divided into six different chemical groups (Table 7). The first-generation as well as the second-generation antihistamines can be categorised into these groups. The second-generation drugs are generally non-sedating, although exceptions have been shown.

Terfenadine and astemizole were withdrawn worldwide because of serious cardiovascular adverse events (torsades de pointes) especially when combined with cytochrome P450 3A4 inhibitors. With polydrug use, pharmacokinetic interactions are more likely and may increase the adverse effects (such as sedation) if the metabolism of the antihistamine is inhibited.

Effects

It should be noted that allergic rhinitis and allergic diseases in general can cause sleep disturbances. Baiardini et al. (2006) examined the effects of respiratory allergies, allergic skin disorders and anti-allergy drugs on sleep. A high prevalence of sleep disturbance was observed. The cognitive effects of allergic rhinitis and its treatment were reviewed by Bender (2005), who noted the deleterious effects on cognition and performance. The author concluded, however, that it was not clear whether the increased alertness that results from the drug's histamine receptor-blocking effect offsets the sedative effect of the medication, or whether there is a combined sedating effect of the antihistamine and the disease. Impairments in vigilance and cognitive functioning associated with allergic rhinitis were studied by Wilken et al. (2002), who also concluded that there is a decrease in speed and efficiency across several cognitive domains. The experimental studies discussed below are summarised in Table A9 (Appendix).

TABLE 7
Overview of the different types of antihistamines

Chemical class	First-generation antihistamines	Second-generation antihistamines
Ethanolamines	Carbinoxamine, clemastine, diphenhydramine, dimenhydrinate, triprolidine	
Ethylenediamines	Pyrilamine, tripelennamine	
Alkylamines	Chlorpheniramine, brompheniramine	Acrivastine
Piperazines	Hydroxyzine, cyclizine, meclozine, buclizine, cinnarizine, oxatomide	Cetirizine, levocetirizine
Phenothiazines	Promethazine, mequitazine, oxomemazine, alimemazine	
Piperidines	Cyproheptadine, pizotifen, ketotifen, phenindamine	Levocabastine, loratadine, desloratadine, fexofenadine, ebastine, terfenadine (1), astemizole (1), rupatadine
Phthalazinones	Azelastine	

(1) Withdrawn from the market in 1998 and 1999.

First-generation antihistamines

Diphenhydramine

Tolerance to the sedative effects of antihistamines was studied by Richardson et al. (2002). Both objective and subjective measures of sleepiness showed significantly higher levels on day 1 for diphenhydramine compared with placebo. By day 4, however, levels of sleepiness on diphenhydramine were indistinguishable from placebo. Similarly, diphenhydramine produced significant impairment of performance that was completely reversed by day 4.

Turner et al. (2006) compared the sedation and memory impairment associated with a single dose of diphenhydramine (50, 75 or 100 mg) or lorazepam (0.5 or 1.5 mg). The tests included memory recall, DSST and CRT. All doses of diphenhydramine impaired subjects' results on the DSST and CRT and caused subjective sedation. Lorazepam 0.5 mg had no effect on any test, while lorazepam 1.5 mg impaired subjects' results on the DSST and CRT and caused subjective sedation. Both diphenhydramine 100 mg and lorazepam 1.5 mg impaired memory recall. Therefore, sedation is not always associated with impaired memory.

Clemastine

A study by Meltzer et al. (2003) on the safety and efficacy of combined administration of pseudoephedrine plus paracetamol versus the combination of clemastine 0.68 mg, pseudoephedrine 60 mg and paracetamol 1 000 mg showed a higher degree of somnolence with the latter.

Mequitazine

A literature search by Didier et al. (2000) concluded that classification based on the chemical structure alone may be misleading, as in the case of mequitazine, which shows a low sedation profile even though it is a first-generation antihistamine. Mequitazine 5 mg twice a day versus dexchlorpheniramine 6 mg, chlorpheniramine 4 mg twice a day, brompheniramine 12 mg twice a day and hydroxyzine 25 mg twice a day produced less or no greater sedation than placebo. Mequitazine 5 mg did not produce more CNS side-effects than the second-generation antihistamines cetirizine, loratadine 10 mg and astemizole 10 mg.

Theunissen et al. (2006a) compared the effects of mequitazine 5, 10 or 15 mg , cetirizine 10 mg, dexchlorpheniramine 6 mg or placebo on two actual driving tests (highway driving and car-following test) and cognitive and psychometric tests (tracking, divided attention, memory, reasoning and CFF). Cetirizine did not affect performance on any task, while mequitazine increased SDLP and affected divided attention and reaction time in a dose-related manner. Dexchlorpheniramine impaired driving performance, as indicated by a significant rise in SDLP. It was concluded that mequitazine is mildly sedating.

Chlorpheniramine

Mochizuki et al. (2002) used PET to determine how chlorpheniramine 6 mg, compared with placebo, affects different regions of the brain. The alterations observed in cortical and subcortical activity caused impairment in spatial cognition.

Chlorpheniramine has major adverse effects on the CNS. According to Serra-Grabulosa et al. (2002), the patient

may not even be aware of this. The authors suggest that, because of the nature of the adverse effects, the prescribing of chlorpheniramine may need to be reviewed. These authors found, for example, that the use of dexchlorpheniramine 4 mg can lead to auditory attention impairment, but that patients were unaware of this side-effect (Serra-Grabulosa et al., 2001).

Tashiro et al. (2008) examined regional cerebral blood flow (rCBF) responses during a simulated car-driving task following oral administration of *d*-chlorpheniramine using PET, based on a single-blind crossover study-design. They found that the number of lane deviations significantly increased in the *d*-chlorpheniramine condition compared with the placebo condition ($p < 0.01$). Subjective sleepiness was not significantly different between the two drug conditions. Diminished brain responses following *d*-chlorpheniramine treatment were detected in the parietal, temporal and visual cortices and in the cerebellum whereas regional cerebral blood flow responses in the orbitofrontal cortex and cerebellar vermis were found to be augmented. These results suggest that *d*-chlorpheniramine tends to suppress visuospatial cognition and visuomotor coordinating functions rather than attention and motor functions during car driving.

Cinnarizine

Subjects' performance after taking cinnarizine 15, 30 or 45 mg was examined by Nicholson et al. (2002), with promethazine 10 mg used as an active control. The performance assessment included DSST and vigilance. Cinnarizine 15 mg had no effects on performance, while cinnarizine 45 mg caused impairment.

A study of antivertiginous medications by Philipova et al. (2004) found no evidence of impairment of reaction time in participants who took four doses of cinnarizine 20 mg or dimenhydrinate 40 mg in a 24-hour period.

Another study of antivertiginous medications, by Schneider et al. (2003), also found no performance effects. This study compared cinnarizine 20 mg plus dimenhydrinate 40 mg with dimenhydrinate 50 mg plus betahistine 12 mg.

Second-generation antihistamines

Desloratadine

Desloratadine is the active metabolite of loratadine. Several studies have examined its effects on performance and vigilance. Nicholson et al. (2003) concluded that desloratadine 5 mg has no effect on daytime sleep latencies and subjective sleepiness, and no adverse effects on psychomotor performance. The study was a crossover design with promethazine as an active control. Assessments were made 1 hour before and from 0.5 to 8 hours after ingestion. Promethazine impaired tracking, CRT and DSST, and increased objective and subjective sleepiness. Desloratadine did not change any of these parameters.

A safety and efficacy study of desloratadine 5 mg in asthma patients by Berger et al. (2002) revealed an adverse event rate similar to that associated with placebo; Monroe et al. (2003) concluded the same in a study of patients with chronic idiopathic urticaria.

In a study that simulated 'real-world' performance tasks, desloratadine either completely restored performance to the level of the asymptomatic placebo-treated control group or improved performance where it had been diminished in subjects with seasonal allergic rhinitis (Satish and Streufert, 2003; Satish et al., 2004).

Valk et al. (2004) tested, in conditions that simulated cabin pressure at 8 000 feet (about 2 400 m) altitude, desloratadine 5 mg, diphenhydramine 50 mg and placebo, all in single doses on different days with 7-day washout periods in between. Measurements included vigilance and tracking, a multi-attribute task battery, the Stanford sleepiness scale and pulse oximetry. The use of desloratadine 5 mg led to no detrimental effects on performance associated with flying ability, which was not the case with diphenhydramine.

In a systematic review, Bousquet et al. (2004) concluded that desloratadine met the European Academy of Allergology and Clinical Immunology's criteria for efficacy, safety and pharmacology of antihistamines. The safety parameters included an evaluation of cognitive and psychomotor impairment associated with use of the drug.

A review article by Berger (2005) evaluated the CNS safety of desloratadine and concluded that it caused no significant CNS-related adverse events.

A similar conclusion was reached by Limon and Kockler (2003), who reviewed studies published between 1966 and 2002.

Loratadine

A comparison of the administration of loratadine 10 mg or rupatadine 10 or 20 mg by Saint-Martin et al. (2004)

showed that more somnolence occurred in the subjects who consumed rupatadine.

Ebastine

Herberg (2000) investigated the effects of ebastine on safety in everyday life and road traffic. The effects of ebastine 10 and 20 mg were evaluated using computer-aided test procedures on days 1, 2 and 7 following administration. Ebastine 10 or 20 mg did not cause more adverse events than placebo, nor did it impair performance. Ebastine 10, 20 or 30 mg was compared with both placebo and triprolidine 10 mg (active control) by Hindmarch and Shamsi (2001), who concluded that the effects of ebastine at all doses were not different from those of placebo on any of the objective tests. The tests included CFF, CRT, a simulated car tracking task, the Sternberg test, LARS and subjective evaluation of sleep.

Levocetirizine

Hair and Scott (2006) reviewed the studies on the pharmacodynamics, pharmacokinetics, therapeutic efficacy and tolerability of levocetirizine. No significant effect on cognition and psychomotor performance was found with the 5-mg dose. Tolerability was good, but the incidence of somnolence was higher than with placebo (5.2 % versus 1.4 %; but no statistical analysis of the difference was reported).

Cetirizine

The effects of different doses of cetirizine (2.5, 5 or 10 mg) on cognitive and psychomotor functions were evaluated by Shamsi et al. (2001) and compared with the effects of loratadine (10, 20 or 40 mg) and promethazine 25 mg. The test battery included CFF, CRT, a compensatory tracking task and assessment of subjective sedation. Administration of cetirizine 10 mg did not lead to disruptive effects on aspects of psychomotor and cognitive function.

A comparison of cetirizine 10 mg and rupatadine 10 mg found no difference between groups in the rates of adverse event rates, including somnolence, the prevalence of which was as high as 9.6 % among the subjects who received cetirizine (Martínez-Cócera et al., 2005).

However, a case report by Nordness and Zacharisen (2003) revealed no sedation or somnolence in a patient taking 50 mg cetirizine a day.

In another study, subjects taking cetirizine 10 mg showed less impairment of performance on a standardised driving test than those taking emedastine 2 or 4 mg twice daily (Vermeeren et al., 2002b). The driving impairment on the first, fourth and fifth days was significant for both doses of emedastine. On the fifth day, alcohol was given before the test in order to achieve a BAC of 0.5 g/l. Alcohol combined with cetirizine or emedastine increased impairment on every test. Women were more impaired than men by both drugs.

Fexofenadine

Fexofenadine 360 mg, promethazine 30 mg and placebo were evaluated in a crossover, double-blind study (Hindmarch et al., 2002). The test battery consisted of CFF, CRT, a compensatory tracking test and a subjective assessment of sedation. The effects of fexofenadine were not different from those of placebo in any of the tests, whereas the use of promethazine significantly impaired all measures. Even at the high dose of 360 mg, fexofenadine had no disruptive effects on psychomotor and cognitive function. In another study, Ridout and Hindmarch (2003) examined the effects of fexofenadine 60 or 120 mg, promethazine 25 mg and placebo. Here, too, fexofenadine use did not lead to cognitive or psychomotor impairment.

Some studies have shown that fexofenadine has mildly stimulating properties. Theunissen et al. (2006b) investigated whether this was the result of the inhibition of dopamine reuptake. The subjects in their study, who received fexofenadine 360 mg or placebo, performed a DSST and a stop signal task. The authors concluded that fexofenadine use improved performance on the DSST but did not potentiate dopamine level in the striatum. They suggested that the activating effects of fexofenadine may be a result of the involvement of H_3 receptors and/or GABA receptors.

In a study by Ridout et al. (2003a), the use of fexofenadine 180 mg with or without alcohol (BAC of 0.3 g/l) had no effect on performance, whereas the use of hydroxyzine produced significant impairment on CFF, RRT and TRT. The combination of hydroxyzine with alcohol also impaired MRT. The test battery included CFF, RRT, MRT, TRT and BRT.

According to Mohler et al. (2002), fexofenadine can be safely used in individuals such as pilots who are involved in skilled activities, without the concern of sedation at or above the recommended doses.

Mizolastine

Bachert et al. (2001) studied treatment with mizolastine 10 mg, and concluded that the incidence of adverse events was low.

Azelastine

The effect of topical azelastine was studied by Golden et al. (2000), who did not find that azelastine causes daytime somnolence.

Within-group comparisons

A review article on the adverse reaction profiles of second-generation antihistamines by Lange and Bachert (2004) evaluated sedative potential as well as cardiotoxicity, hepatotoxicity and teratogenicity. Cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine and mizolastine were included in the review. Cetirizine, levocetirizine and mizolastine were associated with the highest incidence of sedative adverse reactions, whereas desloratadine, ebastine and fexofenadine exhibit few sedative effects.

A placebo-controlled comparison of fexofenadine 120 mg, cetirizine 10 mg and hydroxyzine 30 mg (as positive control) found no significant impairment associated with fexofenadine use relative to placebo, although there was a tendency for use of cetirizine to cause increased sleepiness (Tashiro et al., 2004). Fexofenadine was less impairing than cetirizine on some tasks. Measurements included the Stanford sleepiness scale (subjective sleepiness) and objective psychomotor tests (SRT, CRT and visual discrimination tests).

A study by Takahashi et al. (2004) evaluated the effects of bepotastine 10 mg twice daily, cetirizine 10 mg, fexofenadine 60 mg twice daily and olopatadine 5 mg twice daily on wheal and flare response, sedation and psychomotor performance. A visual analogue scale was used to measure sedation and a word processor test was used to assess psychomotor activity. Olopatadine, fexofenadine and cetirizine all showed a significant sedative effect, increasing in that order, while bepotastine had the least effect. Psychomotor performance was most markedly affected by olopatadine, followed by fexofenadine and cetirizine.

Passalacqua and Canonica (2005) reviewed comparative studies of levocetirizine and desloratadine. Neither drug was shown to alter memory, divert attention, decrease alertness or impair performance.

A study of cetirizine 10 mg versus loratadine 10 mg found less somnolence in patients taking loratadine and better motivation during the day (Salmun et al., 2000).

Inter-drug differences in sedation caused by antihistamines are discussed by Shamsi and Hindmarch (2000). They used proportional impairment ratios for objective evidence to rank the antihistamines, calculating an impairment index for each antihistamine and comparing it with the impairment index obtained for all antihistamines. Fexofenadine, ebastine and astemizole ranked the highest in terms, i.e. caused no impairment, while promethazine ranked the lowest (caused most impairment).

A prescription event-monitoring study found that four second-generation antihistamines (cetirizine, fexofenadine, loratadine and acrivastine) resulted in an overall low incidence of sedation (Mann et al., 2000). The authors suggest that people working in safety-critical jobs who need antihistamines be given fexofenadine or loratadine.

A letter by Ramaekers and Vermeeren (2000) states that ebastine, fexofenadine, loratadine and terfenadine do not have any effects on driving performance when given at the recommended doses, but have at least measurable effects with doses that are twice as high. They also noted that these higher doses are often used by patients with seasonal allergic rhinitis and urticaria.

Layton et al. (2006) conducted a prescription event-monitoring study and concluded that the rates of drowsiness and sedation are low for desloratadine and levocetirizine. However, patients prescribed levocetirizine were more likely to experience drowsiness and sedation in the first month of observation.

Between-generation comparisons

In a review designed to help physicians select the 'optimal' oral antihistamine for their patients, Meltzer (2005) found no impairment associated with fexofenadine even at high doses, impairment only at high doses with use of desloratadine or loratadine and impairment at every dose with cetirizine use. A strong sedating effect was found for clemastine and diphenhydramine, while brompheniramine, chlorpheniramine and cetirizine (at a high dose) produced a moderate effect. Desloratadine and loratadine were not associated with sedating effects, except at high doses, and effects were small. Fexofenadine was free of sedative effects at any dose.

Fexofenadine 120 mg, compared with hydroxyzine 30 mg, had no influence on BRT when driving and using a mobile phone, while hydroxyzine did slow BRT (Tashiro et al., 2005).

An evaluation of the effects of fexofenadine 180 mg, diphenhydramine 50 mg and placebo on the test of variables of attention found no significant effect associated with fexofenadine, which was in contrast to the results for diphenhydramine (Mansfield et al., 2003). Bower et al. (2003), who evaluated fexofenadine for safe use by aviation personnel, found that the psychomotor effects following a single dose of the drug were no different from those with placebo administration.

An evaluation of the acute effects of fexofenadine 120 mg, olopatadine 10 mg and *d*-chlorpheniramine versus placebo on psychomotor function found no effects of fexofenadine on any of the parameters, whereas *d*-chlorpheniramine and olopatadine had sedating effects on psychomotor performance (Kamei et al., 2003).

An analysis of the differential cognitive effects of ebastine 10 mg or chlorpheniramine 2 or 6 mg versus placebo revealed no cognitive impairment with use of ebastine 10 mg (Tagawa et al., 2002). Chlorpheniramine, however, even at the lower dose of 2 mg, produced cognitive function impairment; there was a clear dose–response relationship.

In a comparison of diphenhydramine 50 mg, loratadine 10 mg and placebo, diphenhydramine was found to produce substantial adverse effects on divided attention, working memory, vigilance and speed (Kay, 2000; Kay and Quig, 2001). There was no difference between loratadine and placebo. Although testing on days 3 and 5 showed some equilibration between the active treatment groups, diphenhydramine generated more errors on the divided attention test. The authors concluded that individuals may not be aware of their reduced level of functioning. A study of desloratadine 5 mg versus diphenhydramine 50 mg by Wilken et al. (2003) found that desloratadine alleviated the symptoms of ragweed-induced allergic rhinitis without adversely affecting performance.

Barbanoj et al. (2006) investigated the combined effects of antihistamines with alcohol on seven psychomotor performance tests (e.g. CFF and reaction time). The greatest impairment was seen with the combination of hydroxyzine 25 mg and alcohol 0.8 g/l. When rupatadine 10 mg plus alcohol was administered, the impairment was not greater than with alcohol alone. Alcohol plus cetirizine 10 mg or rupatadine 20 mg produced more impairment than alcohol alone, albeit less than with hydroxyzine. Subjects taking hydroxyzine or cetirizine were not aware of the increased impairment.

A study of tolerance development after repeated doses of mequitazine 10 mg, cetirizine 10 mg or controlled-release dexchlorpheniramine 6 mg revealed that the driving impairment wears off after 8 days (Theunissen et al., 2006a). Cetirizine did not cause any effect from the start of the study.

Levocetirizine 5 mg, in contrast to diphenhydramine 50 mg, does not significantly affect driving performance (Verster et al., 2003a). Subjects underwent a standardised driving test, and SDLP was analysed. In another study, the same authors found no influence of levocetirizine 5 mg on memory, attention or tracking performance after acute or subchronic administration (Verster et al., 2003b). Diphenhydramine 50 mg did, however, significantly affect divided attention and tracking after acute administration.

Vuurman et al. (2004) examined the effects of desloratadine 5 mg, diphenhydramine 50 mg and placebo on a standard driving test 2 hours post dosing. No significant effect of desloratadine on SDLP was noted (whereas this was not the case for diphenhydramine) and BRT was significantly faster following desloratadine administration. Desloratadine did not impair driving performance.

A meta-analysis by Bender et al. (2003) of studies of diphenhydramine and second-generation antihistamines did not find consistent diphenhydramine-induced sedation. The authors concluded that a clear and consistent distinction between sedating and non-sedating antihistamines does not exist.

Weiler et al. (2000) compared the effects on driving of placebo, fexofenadine 60 mg, diphenhydramine 50 mg and alcohol 1 g/l (BAC). Driving performance was assessed with a 1-hour driving simulation. Fexofenadine had the same effect as placebo, whereas diphenhydramine had an even greater impact on driving performance than alcohol.

An analysis by Verster and Volkerts (2004b) shows that the use of first-generation antihistamines is associated with significant impairment, even with repeat administration. Second-generation antihistamines may also impair driving performance, but the magnitude and extent depends on dose, the subject's sex and the time between testing and administration. The second-generation antihistamines fexofenadine and levocetirizine do not cause driving impairment.

Hindmarch et al. (2001b) compared the effects of levocetirizine 5 mg, cetirizine 10 mg, loratadine 10 mg, promethazine 30 mg and placebo on tests that included CFF, CRT, a continuous tracking task and subjective rating scales for sedation (LARS). Levocetirizine and cetirizine were found to have no effect, even after repeated doses, on psychomotor and cognitive functions.

A review of the evidence for impairment by Moskowitz and Wilkinson (2004) states that first-generation antihistamines produce objective performance impairment, as well as subjective symptoms of sedation. This may also be the case with some of the second-generation drugs in some individuals. Within each group, there are substances that lead to less sedation and driving-related performance impairment.

Vuurman et al. (2007) compared the acute effects of rupatadine 10 mg, relative to placebo and 50 mg hydroxyzine (as an active control), on healthy subjects' driving performance. There was no significant difference in SDLP between the rupatadine and placebo groups; however, hydroxyzine treatment significantly increased SDLP. Subjects reported negative effects after receiving hydroxyzine but not after receiving rupatadine.

Conen et al. (2011) demonstrated that 50 mg hydroxyzine significantly increased SDLP on days 1 and 8 of treatment. Bilastine, a new second-generation H_1 antagonist (20 and 40 mg), did not affect SDLP. Hydroxyzine produces severe driving impairment after single doses, and this impairment is only partly mitigated over time owing to a lack of complete tolerance.

Meta-analysis of experimental studies

Table 8 summarises the results of the large meta-analysis of the experimental studies in the DRUID project.

Risks

Accident risk

No recent epidemiological studies specifically investigating the accident risk associated with antihistamines were found. Some studies, however, have assessed the possible association between antihistamines and injuries in general. Finkle et al. (2002) showed that the percentage of injuries attributable to diphenhydramine was 55 % (compared with before use and with loratadine use). Hanrahan and Paramore (2003) found an elevated acute injury risk after exposure to sedating antihistamines (OR 2.93).

Responsibility analyses

One responsibility analysis was found that calculated the risk of responsibility for a traffic accident while under the influence of psychoactive drugs, including sedating antihistamines, but also TCAs, phenothiazine antipsychotics, phenytoin and carbamazepine (Drummer et al., 2004). The results showed that driving under the influence of these psychoactive drugs alone is associated with an increased risk of responsibility for a traffic accident (OR 3.8; 95 % CI 1.3–11).

In a French registry-based study on the risk of road traffic crashes in people who were prescribed medicines, Orriols et al. (2010) found an OR of 1.05 (95 % CI 0.81–1.35) for antihistamines (class R06 in the ATC classification).

TABLE 8

Results of the large meta-analysis of the experimental studies in the DRUID project

	Diphenhydramine	Triprolidine	Terfenadine	Loratadine	Fexofenadine
Number of studies/number of effects	28/481	14/233	16/259	13/213	5/170
Dose (mg)	50	2.5	60	10	120–180
Maximum percentage of impaired results	41	60–70	0.5	1	0
Time (h) of maximum impairment	1.75	1.5–2.5	0	0	0
Duration (h)	7.75	5	0	0	0
Equivalent BAC (g/l)	0.5–0.8	> 0.8	0	0	0
Degree of impairment (1)	92	–	0	0	0
Concentration equivalent to BAC 0.5 g/l	60	5.7	–	–	–

(1) The time that a subject who has taken the drug is impaired by more than 15 % (equivalent to a BAC of 0.3 g/l) in arbitrary units.
NB: –, too few data to calculate the number. If multiple doses were given, only the highest is given in this table. Abbreviation: BAC, blood alcohol concentration.

Meta-analysis

In the meta-analysis of 66 publications by Elvik (2013), the best estimate of the relative risk of accident involvement with antihistamines, adjusted for publication bias, was 1.12 (95 % CI 1.02–1.22) for injury accidents.

Conclusion

Acute effects: Among the first-generation antihistamines, mequitazine seems to be associated with less sedation than the other substances in this group. Diphenhydramine and chlorpheniramine clearly show impairment of psychomotor performance. Clemastine has proven sedative effects. Among the drugs of the second generation, fexofenadine, even at high doses, is not associated with impairment, as is the case with ebastine. Desloratadine and loratadine are free of any disruptive effects on psychomotor performance and they also do not lead to sedation. Cetirizine use can result in a certain degree of impairment, although the studies show contradictory results. Levocetirizine shows a profile similar to that of desloratadine. Drivers should preferably be prescribed antihistamines that do not cause impairment. Based on the studies discussed above, it seems that bilastine, desloratadine, ebastine, fexofenadine, levoceterizine and rupatadine are the safest options. In addition, topical azelastine does not appear to have an effect on vigilance.

Duration of effects: In the case of the antihistamines that impair driving, the maximum impairing effect occurs 2 hours after intake, and the effect can last up to 8 hours.

Combinations: Alcohol can have an additive effect on antihistamines in terms of sedation and psychomotor impairment. Fexofenadine does not potentiate the effects of alcohol and vice versa.

Chronic use: Tolerance to diphenhydramine was found to be complete by the end of 3 days of administration. In the case of mequitazine 10 mg, cetirizine 10 mg or controlled-release dexchlorpheniramine 6 mg, driving impairment wore off after 8 days. Tolerance is incomplete for hydroxyzine.

Threshold concentration: The concentration equivalent to a BAC of 0.5 g/l was calculated as 60 ng/ml diphenhydramine and 5.7 ng/ml triprolidine.

Accident risk: In a meta-analysis the relative risk of accident involvement with antihistamines was 1.12 for injury accidents.

Antidepressants

Antidepressants are substances commonly prescribed for mood disorders, anxiety and sometimes pain. These substances commonly inhibit the reuptake of norepinephrine and/or serotonin and/or, to a minor extent, dopamine. There are first- and second-generation antidepressants and an atypical group (Table 9). The second-generation drugs are associated with fewer adverse effects than the first generation, mainly because of greater selectivity. Adverse effects encountered in the first generation are anticholinergic effects (dry mouth, gastric distress, blurred vision and urinary retention), cardiovascular effects (palpitations, hypotension, tachycardia and arrhythmia) and sedation (with the serotoninergic compounds), while second-generation selective serotonin reuptake inhibitors (SSRIs) are more prone to causing gastrointestinal disturbances and sexual dysfunction.

Acute effects

Table A10 (Appendix) summarises the experimental studies discussed below.

First generation

Few studies have been conducted on the use of TCAs alone after 1999. However, previous studies show that these substances are associated with clear impairment. According to the International Council on Alcohol, Drugs and Traffic Safety classification ([5]), TCAs cause minor or moderate effects, except for trimipramine, amitriptyline, doxepin, dosulepine and amoxapine, which can produce severe adverse effects and are potentially dangerous.

A study by Podewils and Lyketsos (2002) revealed that TCA use is not related to cognitive deficits, nor does it appear to significantly compromise memory (measured by MMSE) over a prolonged period.

Veldhuijzen et al. (2006b) studied the effects of a nocturnal dose of amitriptyline 25 mg on actual driving. At the start of the therapy, a significant increase in SDLP was noted, higher than with a BAC of 0.5 g/l. In addition,

([5]) See http://www.icadts.org/reports/medicinaldrugs1.pdf and http://www.icadts.nl/reports/medicinaldrugs2.pdf for the list of drugs.

TABLE 9
Overview of the different kinds of antidepressants

Class	Mechanism of action	Examples
First generation (tricyclic antidepressants)	Noradrenergic	Nortriptyline, desipramine, protriptyline, maprotiline, amoxapine
	Serotoninergic	Amitriptyline, clomipramine, doxepin, imipramine, trimipramine, dosulepine, melitracen
Second generation	Selective serotonin reuptake inhibitor	Paroxetine, sertraline, citalopram, escitalopram, fluvoxamine, fluoxetine
	Norepinephrine reuptake inhibitor	Reboxetine, atomoxetine
	Serotonin/norepinephrine-reuptake inhibitor	Venlafaxine, milnacipran, duloxetine
Atypical		Trazodone, nefazodone, bupropion, mianserin/mirtazapine, tianeptine/ amineptine
Monoamine oxidase inhibitors (MAOIs)		Selegiline (MAOI-B), phenelzine (MAOI-A), tranylcypromine (MAOI-A), moclobemide (RIMA)

Abbreviation: RIMA, reversible inhibitor of MAOI-A.

reaction times increased significantly. In contrast, after 2 weeks of treatment, no differences were found compared with placebo, suggesting tolerance.

Iwamoto et al. (2008a) detected a significant positive correlation between plasma amitriptyline concentration and road-tracking performance ($r = 0.543$; $p < 0.05$). There was no significant correlation between plasma amitriptyline concentration and other driving performance, cognitive functions or subjective somnolence.

Second generation

SSRIs

A review by Dumont et al. (2005) showed that low doses of an SSRI in healthy volunteers stimulate attention and memory, while high doses tend to impair visual/auditory visuomotor systems and subjective performance, but cause acceleration of motor function. The CFF test showed the most pronounced effect.

Fluoxetine 20–60 mg has been shown to have no effects on cognitive performance on the visual verbal learning test, concept shifting task, letter–digit substitution test and a Stroop colour–word test after 9 weeks of treatment (Strik et al., 2006).

SSRIs do not always result in memory improvement in healthy subjects. Rose et al. (2006) studied the effects of escitalopram 10 mg and found no effects on cognitive or haemodynamic functions. However, Wadsworth et al. (2005) found SSRI use to be associated with memory impairment.

Additional dopamine reuptake inhibition can attenuate vigilance impairment (Schmitt et al., 2002). Sertraline 50–100 mg was compared with paroxetine 40–60 mg using a vigilance test and a Stroop test. Paroxetine, but not sertraline, impaired vigilance. Neither drug resulted in impairment on the other tests. Sertraline is known to block dopamine reuptake.

Sertraline 50–75 mg was shown by Constant et al. (2005) to have beneficial effects on psychomotor slowing and on attentional and executive functions, even after 1 week of treatment, whereas a study by Devanand et al. (2003) found little improvement in cognitive function with sertraline 50–200 mg.

Acute intravenous administration of citalopram 10 mg was associated with increased memory consolidation on an auditory verbal learning test (Harmer et al., 2002).

A study of fluoxetine 20–60 mg and paroxetine 20–40 mg showed no deterioration in cognition; in fact, most of the tested cognitive functions were improved (Cassano et al., 2002).

Abrupt discontinuation of an SSRI can result in a syndrome of adverse effects. According to Hindmarch et al. (2000a), discontinuation only of paroxetine, and not of any other SSRI, leads to a deterioration in various aspects of health and functioning.

The effects of depression and antidepressant therapy on driving performance were evaluated in the Immortal study (Schmitt et al., 2004). The results showed that performance on the SDLP test improved during SSRI use (6–52 weeks). However, performance was still significantly worse than that of the healthy control

subjects. As for cognitive function, there was no significant difference in performance between healthy individuals and those taking antidepressants, except for a reduction in the CFF threshold in the subjects taking antidepressants.

In a review of the literature on the role of SSRIs in traffic safety, Ravera et al. (2012) selected 10 articles as background information on driving-related adverse effects and 15 articles reporting the results of experimental and pharmacoepidemiological studies. The most commonly reported undesirable effects relevant to driving impairment were anxiety, agitation, sleep disturbances, headache, increased risk of suicidal behaviour and deliberate self-harm. Inconsistencies were found between the outcomes of the selected experimental and epidemiological studies and between the two existing categorisation systems under evaluation.

Serotonin–norepinephrine reuptake inhibitors

Venlafaxine had no significant effect on SDLP and failed to impair psychomotor performance in a study by O'Hanlon et al. (1998). However, serious withdrawal symptoms may occur within hours of cessation or reduction of the usual dose and may affect motor and coordination skills to such a degree that patients should be explicitly urged either to adhere to a strict medication routine or not to drive a car (Campagne, 2005).

Milnacipran use was evaluated in young and elderly volunteers by Hindmarch et al. (2000b). Milnacipran 25 or 50 mg had no performance effects in young people, but significantly raised CFF scores in the elderly. Amitriptyline, in contrast, lowered CFF threshold and increased both CRT and errors in compensatory tracking. Poirier et al. (2004) tested the effect of milnacipran on memory and vigilance (CFF and CRT). Milnacipran was shown to be free of any disruptive effects on cognitive function in young and elderly volunteers. In the latter group it seemed to improve performance on the CFF. Repeated administration of milnacipran 50 mg twice daily had no effects on cognitive function (Richet et al., 2004). The authors concluded from the results on laboratory tests and a 'real' on-road driving test that milnacipran 50 mg twice daily does not affect the psychomotor functions required for driving. The drug did not accentuate the negative effects of alcohol.

Within-generation comparisons

A study comparing fluoxetine 10–40 mg with reboxetine 4–8 mg found no difference in reversal of memory impairment (Gallassi et al., 2006). Therapy with either substance led to a significant but incomplete improvement in memory impairment.

A comparison between SSRIs (sertraline, paroxetine, citalopram) and a serotonin–norepinephrine reuptake inhibitors (SNRI) (venlafaxine) shows that both classes of antidepressants impair driving performance (on SDLP and CFF) (Wingen et al., 2006a). However, the authors remarked that this impairment is probably due to residual depressive symptoms.

Brunnauer et al. (2008) studied the effect of reboxetine or mirtazapine on fitness to drive according to the German guidelines for road and traffic safety. Before the institution of treatment with antidepressants, about 65 % of patients did not reach the threshold for safe driving; after 14 days' treatment with reboxetine or mirtazapine patients' driving ability improved. Performance on tests measuring selective attention and reactivity improved significantly in both patient groups (all $p < 0.01$). Furthermore, the frequency of accidents in the risk simulations markedly decreased in patients receiving mirtazapine and reboxetine (all $p < 0.05$). No statistically significant differences between treatment groups were found.

Brunnauer and Laux (2013) performed a systematic review of 21 studies (1980–2011) of driving performance in subjects administered commonly prescribed newer antidepressants. Investigations were frequently undertaken in an ambulatory setting in healthy subjects, predominantly young males, and focused on the acute or subchronic effects. Agomelatine, duloxetine, bupropion and viloxazine were found to have no effects. There was also evidence that the SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, paroxetine) and the SNRI venlafaxine have no deleterious effects on driving ability. In contrast, acute use of mirtazapine does cause impairment, but this is diminished to some degree when given at night and is not apparent after repeated dosing in healthy control subjects. Patients obviously benefit from treatment with newer antidepressants; however, at least a subgroup does not reach the performance level of healthy subjects.

Comparison between generations

Driving performance

The effects on driving performance of use of TCAs and SSRIs are summarised in a review by Ramaekers (2003b). SDLP was assessed during a 1-hour on-the-

road driving test. Sedating antidepressants (TCAs and mianserin) led to an increase in SDLP similar to that associated with a BAC of 0.8 g/l. Nocturnal doses of sedating antidepressants (dothiepin, mianserin and mirtazapine) did not produce residual driving impairment the next morning. Non-sedating antidepressants (moclobemide, fluoxetine, paroxetine, venlafaxine and nefazodone) did not affect SDLP; however, when they were co-administered with a benzodiazepine (with an incompatible pharmacokinetic profile), the SDLP rose to unacceptable levels.

Brunnauer et al. (2006) found that, in terms of fitness to drive, SSRIs and mirtazapine have an advantage over TCAs and the SNRI venlafaxine.

Ridout et al. (2003b) found that paroxetine 20 mg has no effect on BRT and improves CFF and the RRT component of the CRT, while mirtazapine 15 or 30 mg taken at night leads to impaired results on laboratory performance tests.

Cognitive performance

Physical and cognitive symptoms are frequently reported by patients whose major depressive disorder has responded to long-term antidepressant therapy. Fava et al. (2006) concluded that these symptoms are both side-effects of the antidepressant therapy and the residual depressive symptoms. In patients with depression, Kalb et al. (2006) found increased reaction times and reduced error rates compared with healthy control subjects. The antidepressant doses correlated negatively with reaction time but positively with the error rates.

A continuous performance test (CPT) was used by Koetsier et al. (2002) to evaluate the attentional performance of in-patients with depression before and after 4 weeks of taking imipramine (blood level 200–300 µg/l) and fluvoxamine (150–200 µg/l). CPT performance was improved with both drugs, as was the clinical state. However, a clear relationship between the altered CPT and the changes on the clinical scales was absent. A clear difference was seen between desipramine 125–200 mg and fluoxetine 20 mg on memory impairment (Levkovitz et al., 2002). Fluoxetine led to a greater improvement in memory performance than desipramine.

A comparison of the effects of fluvoxamine 100 mg and dothiepine 100 mg on sleep and daytime sleepiness after a single administration showed an alteration of night-time sleep with both drugs (Wilson et al., 2000). More daytime sleepiness was observed with dothiepine use. Fluvoxamine decreased and dothiepine increased total sleep time.

Katona et al. (1999) compared reboxetine 4–6 mg with administration of imipramine 50–100 mg and found no somnolence in the subjects taking reboxetine.

According to a review by Peretti et al. (2000) of SSRIs and TCAs, TCAs with anticholinergic and antihistaminic properties have a greater risk of affecting memory and psychomotor function. CFF was elevated in subjects taking fluoxetine and sertraline, while TCAs decreased the CFF threshold. Paroxetine produced no impairment of performance compared with placebo, while this was not the case with amitriptyline. BRT is not impaired with use of SSRIs but it is with use of TCAs.

Cognitive dysfunction commonly occurs in older persons and is sometimes caused by major depression. Nebes et al. (2003) examined the persistence of cognitive dysfunction after treatment with paroxetine or nortriptyline (information on the doses was not given). Neither antidepressant led to changes in cognitive function, although the subjects showed good clinical outcomes for their depression. However, Doraiswamy et al. (2003) found an improvement in cognitive function and an improvement in the symptoms of the depression with use of sertraline 50 mg, fluoxetine 20 mg or nortriptyline 25 mg. Venlafaxine (37.5 mg twice daily) compared with dothiepine (25 mg in the morning plus 75 mg in the evening) does not lead to disruptive effects on cognitive function in elderly patients with depression (Trick et al., 2004). The tests included CFF, a short-term memory test and a questionnaire assessing cognitive failure. Butters et al. (2000) also found an improvement in specific cognitive domains following antidepressant treatment in elderly subjects, but normal levels of performance were not always reached, particularly in memory and executive functions. The antidepressants used were paroxetine or nortriptyline (dosing information was not given).

In a study by Wingen et al. (2006b), use of escitalopram 10–20 mg did not affect immediate or delayed verbal memory score, while treatment with mirtazapine 30–45 mg led to impairment. The authors suggested that the effects seen with mirtazapine might be due to the antihistaminic effect of the substance.

Compared with nortriptyline 25–100 mg, sertraline 50–100 mg had a more positive effect on verbal learning and recall as well as on visual tracking, coding and motor performance (Coffey et al., 2002). The tests included a shopping list task (recall), DSST and MMSE.

In a double-blind, three-way crossover trial, 17 healthy males received acute doses of 10 mg paroxetine, 25 mg amitriptyline and placebo. At 4 hours post dosing, amitriptyline significantly impaired road-tracking and car-following performance, reduced driver vigilance and caused subjective somnolence. Paroxetine impaired neither driving performance nor cognitive function (Iwamoto et al., 2008b).

Atypical antidepressants

Ridout and Hindmarch (2001) compared the use of tianeptine 12.5 or 37.5 mg (an antidepressant promoting the reuptake of serotonin and related to the TCAs) with mianserin 30 mg and placebo on subjects' performance on the CRT, CFF, BRT and self-assessed ratings of sedation (LARS). Tianeptine proved to be free of any effects, while mianserin use was associated with changes on all of the parameters.

Two studies on *Hypericum perforatum* (St. John's wort) found no effects on cognitive or psychomotor function. Timoshanko et al. (2001) administered 900–1 800 mg of the herb and observed only dose-related impairment on the DSST and no effects on CRT and CFF, while the positive control, amitriptyline 25 mg, impaired subjects' overall performance. Siepmann et al. (2002) found no effect of St. John's wort extract 255–285 mg on cognitive function.

The use of moclobemide 150 mg twice daily does not appear to affect cognitive function (Siepmann et al., 2004). The tests included CFF, CRT and memory.

Shen et al. (2009) investigated the effects of mirtazapine on driving safety in a driving simulator and on daytime alertness in 28 patients who met the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition) criteria for major depressive disorder. Half of these patients took mirtazapine 30 mg at bedtime for 30 days. (The untreated group were studied only at baseline and on days 2 and 9, following which they underwent no further testing and were placed on an active treatment.) There was a significant linear relationship between treatment and road position in trials at all testing times ($p = 0.0018$), and at 10.00 a.m. ($p < 0.001$) and 12.00 p.m. ($p = 0.022$) and between the treatment and the number of crashes in trials at all times ($p = 0.034$) and at the 4.00 p.m. session ($p = 0.050$). Compared with the values at baseline, road position at 10.00 a.m. significantly improved on days 2 ($p < 0.05$), 9 ($p < 0.01$), 16 ($p < 0.01$) and 30 ($p < 0.01$) and road position at 12.00 p.m. significantly improved on days 16 ($p < 0.05$) and 30 ($p < 0.05$). The number of crashes significantly decreased on day 30 ($p < 0.05$). This study showed that mirtazapine can increase driving safety in major depressive disorder patients.

Ramaekers et al. (2011) measured the residual effects of single and repeated doses of esmirtazapine 1.5 and 4.5 mg on actual driving in 32 healthy volunteers in a double-blind, placebo-controlled study. Treatment with single doses of zopiclone 7.5 mg was included as active control. Treatments were administered in the evening. Driving performance was assessed in the morning, 11 hours after drug intake. Esmirtazapine 1.5 mg did not produce any clinically relevant change in SDLP after single and repeated dosing. Driving impairment did occur after a single-dose administration of esmirtazapine 4.5 mg, but this effect was abolished after repeated doses. Acute driving impairment was more pronounced after both doses of esmirtazapine in a select group of poor metabolisers. Single-dose zopiclone 7.5 mg also increased SDLP.

Meta-analyses of experimental studies

Table 10 shows the results of the meta-analysis of the experimental studies in the DRUID project (Berghaus et al., 2010).

TABLE 10

Results of the large meta-analysis of the experimental studies in the DRUID project

	Imipramine	Amitriptyline	Fluoxetine	Paroxetine	Mianserin	Trazodone
Number of studies/number of effects	13/210	32/475	5/150	6/118	8/145	8/146
Dose (mg)	50–150	50	20–60	10–40	10–20	50–100
Maximum percentage of impaired results	20	51	0	< 10	42	44
Time (h) of maximum impairment	6.25	3.25	0	3–5	0.75	2.75
Duration (h)	13.5	23+	0	–	16.25	6.5
Equivalent BAC (g/l)	0.3–0.5	> 0.8	0	< 0.3	0.5–0.8	0.5–0.8
Degree of impairment (1)	32	380	0	0	185	87
Concentration equivalent to BAC 0.5 g/l	–	–	–	–	8.9	1 240

(1) The time that a subject who has taken the drug is impaired by more than 15 % (equivalent to a BAC of 0.3 g/l) in arbitrary units.
NB: –, too few data to calculate the number. If multiple doses were given, only the highest is given in this table. Abbreviation: BAC, blood alcohol concentration.

Risks

Accident involvement

The Immortal study in the Netherlands attempted to evaluate the accident risk associated with TCA use; however, there were too few TCA-positive samples to be able to calculate the risk (Assum et al., 2005). A case–control study in France found that 1.8 % of injured drivers tested positive for antidepressants, while only 1.1 % of control subjects tested positive (Mura et al., 2003). The authors did not calculate accident risk in their study, but our own calculations using their data found that the risk was not significantly increased for these prevalence rates in cases and control subjects.

Meuleners et al. (2011), in a retrospective, population-based, case-crossover study determined the association between psychoactive medications and crash risk in older drivers in Western Australia. A total of 616 individuals aged 60 and older who were hospitalised as the result of a motor vehicle crash between 2002 and 2008 were included. The risk of a crash resulting in hospitalisation was higher among older drivers prescribed antidepressants (OR 1.8; 95 % CI 1.0–3.3) and was significantly higher in men prescribed an antidepressant (OR 2.7; 95 % CI 1.1–6.9). Drivers with a chronic condition taking antidepressants (OR 3.4; 95 % CI 1.3–8.5) also had a greater crash risk.

Bramness et al. (2008) obtained information on prescriptions, road accidents and emigrations/deaths from three Norwegian population-based registries. Data on 3.1 million people between the ages of 18 and 69 were linked. Exposure consisted of receiving prescriptions for any antidepressants. The traffic accident risk increased slightly for drivers who had received prescriptions for sedating antidepressants [TCAs, mianserin and mirtazapine; SIR 1.4 (95 % CI 1.2–1.6)] or non-sedating antidepressants [SSRIs, moclobemide, venlafaxine and reboxetine; SIR 1.6 (95 % CI 1.5–1.7)]. The SIR estimates were similar for male and female drivers and slightly higher for young drivers (18–34 years of age) using older sedative antidepressants. SIR estimates did not change substantially for different time periods after dispensing of the prescription, for concomitant use of other impairing drugs or for new users. No increase in the traffic accident risk after exposure to lithium or valproate was observed, except for young female drivers on lithium. This may be because these drugs carry no increased risk or because patients exposed to these drugs refrain from driving (Bramness et al., 2009).

In an active-duty military population between 2002 and 2006, only antidepressant medications were an independent predictor of fatal motor vehicle crashes (OR 3.19; 95 % CI 1.01–10.07). Male gender, black race, enlisted rank, service branch (navy and marine corps) and selected co-morbidities were also independent predictors. The association between prescribed antidepressants and fatal motor vehicle crashes may reflect unmeasured co-morbidities, such as combined effects of prescribed and over-the-counter medications and/or alcohol or other substance abuse (Hooper et al., 2010).

To estimate the risk of road traffic crashes associated with prescription of antidepressants, a case–control analysis comparing 34 896 responsible versus 37 789 non-responsible drivers was conducted in France (Orriols et al., 2012). A significant association was found between the risk of responsibility for a crash 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 a road traffic crash increased after an initiation of antidepressant treatment (OR 1.49; 95 % CI 1.24–1.79) or a change in antidepressant treatment (OR 1.32; 95 % CI 1.09–1.60).

A record-linkage database was used to perform a case–control study in the Netherlands using pharmacy prescription data, police traffic accident data and driving licence data from 2000 to 2007. A significant association was found between traffic accident risk and exposure to SSRIs (OR 2.03; 95 % CI 1.31–3.14). A statistically significant increased risk was also seen in chronic SSRI users (Ravera et al., 2011).

Responsibility analyses

One responsibility analysis was found that calculated the risk of responsibility for a traffic accident while under the influence of psychoactive drugs, including TCAs, but also sedating antihistamines, phenothiazine antipsychotics, phenytoin and carbamazepine (Drummer et al., 2004). The results showed that driving under the influence of these psychoactive drugs alone is associated with an increased risk of responsibility for a traffic accident (OR 3.8; 95 % CI 1.3–11).

One pharmacoepidemiological study was found that investigated the relationship between responsibility for a traffic accident and antidepressant use in the elderly (McGwin et al., 2000). The use of antidepressants was not associated with an increase in the risk of responsibility for an accident. Pharmacoepidemiological studies that were published before 1999 came to similar conclusions: the use of antidepressants was not associated with an increased risk of hospitalisation (Neutel, 1995) or being involved in a traffic accident (Barbone et al., 1998).

In a case–control study of 733 injured drivers (Hours et al., 2008), diseases and medicine consumption were analysed using logistic regression models. An association between antidepressant consumption and responsibility was observed (adjusted OR 3.61; 95 % CI 1.30–10.03).

In a French registry-based study on the responsibility for road traffic crashes in people who were prescribed medicines, Orriols et al. (2010) found an OR of 1.31 (95 % CI 1.19–1.44) for psychoanaleptics (N06 in the ATC classification; this class includes antidepressants, psychostimulants and antidementia drugs).

Meta-analyses

In the meta-analysis of 66 publications by Elvik (2013), the best estimate of the relative risk of accident involvement with antidepressants, adjusted for publication bias, was 1.32 (95 % CI 1.08–1.70) for injury accidents and 1.28 (95 % CI 0.90–1.80) for crashes resulting in property damage.

Dassanayake et al. (2011) found that the accident risk was higher in the elderly (> 65 years of age) who use TCAs; however, the evidence for an association of antidepressants with accident risk in younger drivers was equivocal. Sedative, but not non-sedative, antidepressants were found to cause short-term impairment of several measures of driving performance.

Conclusion

Acute effects: There is evidence that moclobemide, tianeptine, the SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, paroxetine) and the SNRIs venlafaxine and milnacipran have no deleterious effects on driving ability. Withdrawal symptoms with venlafaxine or paroxetine can cause serious impairment. Acute use of mirtazapine produces impairment that is diminished to some degree when given at night and cannot be seen after repeated dosing in healthy control subjects. TCAs, compared with the more recent antidepressants, cause more impairment of cognition and psychomotor skills. The results of the SSRI studies are not always consistent. Sertraline use was found to be associated with improvement in psychomotor function but most SSRIs had no effect on, or improved, cognitive function. The effects of antidepressants on memory and cognition can be difficult to interpret since depression itself can have detrimental effects on these functions. Resolution of the depression can often also result in resolution of depression-related cognitive deficits. Patients obviously benefit from treatment with newer antidepressants; however, at least a subgroup does not reach the performance level of healthy subjects.

Duration of effects: The time of maximum impairment varies between 1 and 6 hours and impairment can persist for up to 24 hours.

Chronic use: Tolerance to the cognitive and psychomotor effects of TCAs seems to develop with prolonged use. Nevertheless, caution should be advised when prescribing these older substances, since previous studies have clearly demonstrated an impairing effect.

Threshold concentration: The concentration equivalent to a BAC of 0.5 g/l was calculated as 8.9 ng/ml mianserin and 1 240 ng/ml trazodone.

Accident risk: In a meta-analysis the relative risk of accident involvement with antidepressants was approximately 1.30.

Other synthetic psychoactive substances/medicines

Gamma-hydroxybutyrate

Gamma-hydroxybutyrate (GHB) is a normal component of the mammalian CNS. Synthetic GHB was first used as an anaesthetic in the 1960s. In the early 1990s, it was sold in health food stores and marketed as a treatment for anxiety, insomnia and drug and alcohol abuse and for use by athletes and body builders. The United States Food and Drug Administration removed GHB from the market in 1990 following reports of GHB-related coma and seizures (Freese et al., 2002).

Acute effects

Four experimental studies on the acute effects of GHB were found.

Ferrara et al. (1999) examined the subjective, cognitive and motor effects in humans following administration of typical therapeutic doses. Oral doses of 12.5 and 25 mg/kg had no effect on attention, vigilance, alertness, short-term memory or psychomotor skills based on the tests used. The only adverse effects noted were slight dizziness and dullness, and these effects disappeared within 60 minutes.

In a double-blind, placebo-controlled, four-arm, crossover study, Haller et al. (2004) administered to eight healthy adults 50 mg/kg GHB, 0.6 g/l ethanol in two doses, both drugs or placebo. Changes in cognitive performance were assessed using a computerised test battery. GHB impaired specific cognitive tasks: speed of attention, quality of episodic memory and speed of memory. Although decrements in speed of response were identified, the accuracy of those responses was not impaired. Additive, but not synergistic, effects of GHB and ethanol on cognitive impairment were identified.

Carter et al. (2006) investigated the psychomotor and cognitive effects of supratherapeutic doses of GHB (2–18 g/70 kg) and compared them with those of triazolam (0.5 and 1 mg/70 kg) and pentobarbital (200 and 400 mg/70 kg). GHB produced effects similar to triazolam and pentobarbital; however, memory impairment after GHB use was less than that after use of triazolam or pentobarbital. The within-subject dose–effect function for sedation was steeper for GHB than for triazolam or pentobarbital. Furthermore, at higher doses, GHB was associated with greater sedation and more variability between subjects.

Abanades et al. (2006) administered increasing doses of oral sodium GHB (40, 50, 60 and 72 mg/kg) to eight volunteers. The mean peak GHB plasma concentration following doses of 40, 50, 60 and 72 mg/kg was 79.1, 83.1, 113.5 and 130.1 mg/l , respectively. GHB showed a mixed stimulant–sedative pattern, with initially increased scores on measures of subjective feelings of euphoria, 'high' and liking followed by mild–moderate symptoms of sedation with impairment of performance and balance. GHB produced a slight deterioration in psychomotor performance that was apparently dose dependent with a peak effect at 30 minutes after administration of lower doses and at 1.5 hours post administration of the 72-mg/kg dose. A decrease was seen in DSST total responses and DSST correct responses, while there was a simultaneous increase in DSST errors. Doses of 60 and 72 mg/kg were associated with an impairment of the balance task with a peak effect at 1 hour post administration. At all administered doses, GHB induced exophoria, a typical effect of sedatives, as measured by the Maddox wing device.

A few case reports were found on driving under the influence of GHB.

Couper and Logan (2001) described 13 subjects arrested for impaired driving in the United States whose blood samples tested positive for GHB. GHB concentrations ranged from 26 to 155 mg/l (mean 87 mg/l, median 95 mg/l). In eight cases, GHB was the only drug detected, and signs of impairment were consistent with those of a CNS depressant, including erratic driving (weaving, swerving and ignoring road signs), confusion, incoherent speech, unresponsiveness, lack of balance, unsteady coordination, poor performance on field sobriety tests and varying states of wakefulness. The authors concluded that, given the ability of GHB to induce sleep and unconsciousness, these cases show that recreational use of the drug has the potential to impair driving ability. The same authors later described a case report of a 38-year-old man who was arrested seven times over an 8-month period for

driving under the influence of GHB (Couper and Logan, 2004b). Blood GHB concentrations ranged from 44 to 184 mg/l (mean 100 mg/l, median 73 mg/l). The overall signs of impairment included erratic driving (severe lane deviation, collisions and near-collisions), slurred speech, disorientation, slowness to react, shaking, agitation, inability to focus, poor coordination and balance, poor performance in field sobriety tests, somnolence and unconsciousness. On only one occasion were other drugs (thiopental and diazepam) that may have contributed to the observed driving impairment present in the subject's blood.

Bosman and Lusthof (2003) described forensic cases involving the use of GHB in the Netherlands, including 13 cases of driving under its influence. GHB concentrations in subjects' blood ranged from 51 to 195 mg/l and in urine from 100 to 2 000 mg/l. High concentrations of GHB corresponded with extreme sleepiness or temporary loss of consciousness. GHB was considered to have caused driving impairment in all cases.

Al-Samarraie et al. (2010) described 25 car drivers who had tested positive for GHB only in their blood in Norway. The police reported that 78 % showed unsafe driving behaviour and seven were involved in car accidents without serious injury. A total of 61 % of the drivers were found to be sleepy or in an even more reduced state of consciousness. The median GHB blood concentration was 131 mg/l (range 62–228 mg/l), measured a median of 69 minutes after the police had stopped the driver from driving. In Sweden, the mean and median GHB concentrations were 89 mg/l and 82 mg/l, respectively (2.5th and 97.5th percentiles: 12 and 220 mg/l) in 548 arrested drivers (Jones et al., 2008a).

Vindenes et al. (2012) proposed the following limits for graded sanctions: 10 300 µg/l (equivalent to a BAC of 0.2 g/l), 30 900 µg/l (equivalent to a BAC of 0.5 g/l) and 123 600 µg/l (equivalent to a BAC of 1.2 g/l).

No studies were found on the chronic effects or risks associated with the use of GHB.

Conclusion

Acute effects: The limited data that were found for GHB suggest that the range of GHB doses that are typically consumed by users (25–75 mg/kg) can cause dose-dependent cognitive and psychomotor impairment. The results from case reports also indicate impairment following GHB use by drivers, including extreme sleepiness, poor coordination and balance and even unconsciousness.

Duration of effects: The effects of GHB last a few hours.

Combinations: There are additive but not synergistic effects of GHB and ethanol on cognitive impairment.

Chronic use: No studies were found.

Threshold concentration: In Norway the impairment limit was set at 10.3 mg/l.

Accident risk: No risk studies were found.

Ketamine

Ketamine is a synthetic sedative compound that acts as a CNS depressant and produces a rapid dissociative effect.

Acute effects

Several experimental studies that assessed the acute effects of ketamine were found. Curran and Morgan (2000) investigated the cognitive effects of ketamine in recreational users on the night of drug use and 3 days later. Twenty volunteers who reported having taken ketamine were compared with 19 volunteers who reported no consumption of ketamine on the relevant night (day 0). All 39 participants took a battery of tests of memory functions and attention. Doses taken before testing varied from 0.0624 g to 0.5 g, with a mean dose of 0.14 g (± 0.16 g). The ketamine users were profoundly impaired on virtually all objective assessments of cognitive function compared with the control subjects on the day they took the drug. On most objective measures, ketamine users performed at much higher levels on day 3 than on day 0. However, on certain measures, group differences were still highly significant on day 3, namely on the tasks that assessed semantic memory.

Hetem et al. (2000) gave 26 healthy volunteers a 60-minute infusion of ketamine (0.5 mg/kg/h) or placebo. Subjects carried out episodic memory tasks involving words presented before and during infusion. Memory performance was assessed using recognition and free recall tasks. Ketamine impaired performance in free recall and recognition of words presented during, but not before, infusion. Ketamine thus decreased episodic memory performance by impairing the encoding but not the retrieval processes.

Krystal et al. (2000) reported the results of two studies designed to examine the effects of ketamine on WCST performance. In the first study, 15 healthy subjects

completed the WCST on two occasions separated by 1 week. In the second study, 22 healthy subjects completed the WCST and other assessments after administration of ketamine (intravenous bolus 0.26 mg/kg followed by infusion of 0.65 mg/kg/h) or placebo on two test days separated by approximately 1 week. In the first study, the number of total and perseverative errors was reduced on a single repetition of the WCST. In the second study, ketamine significantly increased the number of total errors and the number and percentage of perseverative errors on the first but not the second test day. Similarly, it reduced the number of category criteria met on the first, but not the second, test day. Ketamine also increased distractibility and impaired recall.

Guillermain et al. (2001) investigated the effects of a subanaesthetic dose of ketamine (0.5 mg/kg over 60 minutes) on information processing using a two-choice visual reaction time task. The results showed that ketamine increased CRT and that there was an additive pattern of effects of signal intensity, stimulus response mapping and foreperiod duration on both mean reaction time and reaction time variance.

Honey et al. (2003) investigated the effects of ketamine on executive processes during a working memory task. Eleven healthy volunteers received a different intravenous infusion on each of three occasions: placebo, a low ketamine dose (target plasma concentration of 50 ng/ml) or a high ketamine dose (target plasma concentration 100 ng/ml). Impairments were seen only at the higher dose of ketamine and were restricted to a subgroup of the verbal working memory tasks. While visuospatial working memory and simple maintenance processes during verbal working memory showed no evidence of impairment, the higher dose of ketamine produced a significant impairment in the manipulation of information within working memory.

Morgan et al. (2004a) found that ketamine (infusions of two doses of 0.4 or 0.8 mg/kg) produced a dose-dependent impairment of episodic and working memory and a slowing of semantic processing in healthy volunteers. Ketamine also impaired recognition memory and procedural learning. Attention, perceptual priming and executive functioning were not affected. The same researchers report in another study that the infusions at 0.4 or 0.8 mg/kg acutely impaired response inhibition and episodic memory in healthy volunteers, while semantic memory was not affected; no residual effects were observed 3 days after administration (Morgan et al., 2004b).

Rowland et al. (2005) investigated the cognitive effects of a subanaesthetic dose of ketamine (a loading dose of 0.27 mg/kg over 10 minutes and a maintenance dose of 0.00225 mg/kg/minute for the remainder of the experiment) in healthy volunteers. Ketamine impaired learning of spatial and verbal information, but retrieval of information prior to drug administration was preserved. The drug did not significantly impair attention, verbal fluency or verbal working memory task performance. Spatial working memory was slightly impaired.

Passie et al. (2005) investigated the effects of different subanaesthetic doses of *S*-ketamine (a bolus of 5 mg over 5 minutes for the low- and the high-dose conditions, followed by infusion with 0.003 mg/kg/minute for the low-dose condition and 0.005 mg/kg/minute for the high-dose condition) on neuropsychological tests in healthy male volunteers. The results indicated that both doses produce only non-significant impairment on most of the tasks. Tasks involving divided and sustained attention showed significant impairment in a dose-dependent manner.

Lofwall et al. (2006) administered single intramuscular injections of ketamine (0.2 mg/kg or 0.4 mg/kg) to healthy volunteers. Ketamine selectively impaired free recall while sparing recognition memory, source memory and metamemory. It also disrupted encoding while sparing retrieval processes, impaired working memory performance while sparing attention, and slowed DSST performance while sparing accuracy. Subjective and psychomotor effects were dose dependent and present at a dose (0.2 mg/kg) that did not produce significant memory impairment. Impairment on most of the psychomotor measures dissipated within 2 hours of injection, whereas performance on the CLT and subjective feelings of alertness, drug liking or disliking and drug strength persisted 2.5 hours after injection.

Morgan et al. (2006a) examined whether there were gender differences in response to ketamine in humans, and found that men showed greater impairment in memory after ketamine administration than women. No other gender differences in cognitive measures were found.

Cheng et al. (2007) successfully identified 15 out of a sample of 21 ketamine-only users (71 %) by field impairment testing. When salivary ketamine concentrations were greater than 300 ng/ml, signs of impairment were even more evident, and field impairment testing achieved a detection rate of over 90 %. The typical signs observable in subjects under the influence of ketamine included lack of convergence, horizontal gaze nystagmus, elevated pulse rate and, in general, failing the divided attention tests, especially the walk-and-turn and one-leg stand.

In their meta-analysis performed as part of the DRUID project, Strand et al. (2011) concluded that impairment was observed after intravenous doses of ketamine over 0.1 mg/kg (7 mg), and impairment was apparent at a plasma concentration level of 113 ng/ml. Impairing effects might still be present two half-lives (5 hours) after administration of the lowest therapeutic dose.

Vindenes et al. (2012) proposed the following limits for graded sanctions: 55 µg/l (equivalent to a BAC of 0.2 g/l), 137 µg/l (equivalent to a BAC of 0.5 g/l) and 329 µg/l (equivalent to a BAC of 1.2 g/l).

Combination with other psychoactive substances

Krystal et al. (2005) investigated the effects of administering ketamine (1-minute infusion of 0.23 mg/kg followed by a 1-hour infusion of 0.5 mg/kg) combined with amphetamine (1-minute infusion of 0.25 mg/kg) in healthy volunteers. They found that amphetamine attenuated the impairment of working memory produced by ketamine and that amphetamine and ketamine had additive effects on thought disorder, arousal and euphoria.

Nicotine is known to enhance attention and information processing. Cho et al. (2005) investigated whether nicotine attenuates the deficits in cortical information processing and cognitive functions produced by ketamine (bolus 0.26 mg/kg followed by infusion of 0.65 mg/kg/h). The results indicated that nicotine can attenuate ketamine-induced deficits in information processing and attention.

Chronic effects

Curran and Monaghan (2001) investigated whether the persisting memory impairment 3 days after ingestion of ketamine in recreational users that was assessed by Curran and Morgan (2000) reflects chronic effects. They assessed the effects of ketamine in frequent and infrequent users on the day of ketamine use and 3 days later. On day 3, the frequent users showed significant impairments on tasks assessing episodic and semantic memory compared with the infrequent users. The authors concluded that frequent use of ketamine produces long-lasting impairments in episodic memory and aspects of retrieval from semantic memory. These findings were confirmed in later studies (Morgan et al., 2004c, 2006b). During a 3-year longitudinal investigation of the cognitive and subjective effects of ketamine in recreational users who substantially reduced their use of the drug, Morgan et al. (2004d) found that semantic memory impairments associated with recreational ketamine were reversible upon marked reduction of use. However, impairments of episodic memory and possibly attentional functioning appeared to be long-lasting.

No epidemiological studies were found on the risk of being involved in or responsible for an accident associated with the use of ketamine.

Conclusion

Acute effects: Experimental studies using single subanaesthetic intravenous or intramuscular doses of ketamine indicate that some cognitive and psychomotor functions are affected for up to 2.5 hours, whereas other functions, such as semantic memory, are not affected. Some of these defects are dose dependent.

Duration of effects: Effects last up to 5 hours. Semantic memory was impaired for 3 days.

Combinations: Some of the effects can be attenuated by, for example, amphetamine or nicotine.

Chronic use: Recreational use of ketamine can cause cognitive defects, of which some are reversible and others long-lasting.

Threshold concentration: Dose-dependent impairment was observed at a plasma concentration level of 113 ng/ml. In Norway the impairment limit was set at 55 ng/ml. Signs of impairment became evident when salivary ketamine concentrations were greater than 300 ng/ml.

Accident risk: No studies of accident risks associated with the use of ketamine were found.

Phencyclidine

Phencyclidine (PCP) was first developed for use as an intravenous anaesthesia agent, but was withdrawn from clinical trials because of the occurrence of severe emergence delirium. It was subsequently abused as a recreational drug.

Acute effects

No experimental studies on the acute effects of PCP in humans published in 1999 or later were found. Studies that were published before 1999 showed that a single subanaesthetic dose of PCP (< 20 mg) can induce

severe impairment of cognitive and psychomotor functions lasting up to 14 hours in healthy volunteers (Baselt, 2001).

No studies on the chronic effects or risks associated with the use of PCP were found.

Conclusion

Experimental studies show that single subanaesthetic doses of PCP can cause severe cognitive and psychomotor impairment in healthy volunteers. There is a need for more experimental studies on the acute effects of PCP alone or in combination with other psychoactive substances, and on the chronic effects and accident risks associated with the use of PCP.

Ephedrine

Ephedrine is a naturally occurring stimulant drug similar in structure to amphetamine. It is commonly used as a stimulant, appetite suppressant and decongestant and for treating hypotension associated with regional anaesthesia (Baselt, 2001). Ephedrine is a key precursor of methamphetamine, and is used as a cutting agent in amphetamine powder and in other illicit tablets.

Acute effects

Beversdorf et al. (1999) compared the effects of 40 mg of propranolol (a β-adrenergic antagonist), 25 mg of ephedrine (a β-adrenergic agonist) or placebo on problem-solving in healthy volunteers. On the task that appeared to rely most heavily on cognitive flexibility (anagrams), subjects who were most able to solve these problems demonstrated significantly shorter solution times after propranolol use than after ephedrine. There was a trend towards shorter solution times for ephedrine than for placebo, but this was not statistically significant.

Choi et al. (2006) compared the performance of healthy volunteers on tasks assessing cognitive flexibility, problem-solving and verbal and spatial memory tasks after receiving 0.1 mg of clonidine (an α_2-agonist), 25 mg of ephedrine or placebo. Ephedrine use led to impairment of verbal memory and a non-significant improvement of spatial memory.

No recent studies were found on the effects of ephedrine in combination with another psychoactive substance. Previously, Alkana et al. (1977) found that ephedrine (50 mg) use may partially counteract the adverse effects of alcohol (0.8 g/l).

No studies of the chronic effects of ephedrine were found.

Risks

No studies were found on the risks associated with the use of ephedrine alone. However, two responsibility analyses were found for the risks associated with the use of stimulants, including ephedrine. Drummer et al. (2004) conducted a responsibility analysis in 3 398 fatally injured drivers. They calculated the risks associated with a group of substances acting as stimulants, namely amphetamine, methamphetamine, MDMA, ephedrine, pseudoephedrine, phentermine and cocaine. There was no significant association between use of stimulants and crash responsibility. However, when truckers were considered as a discrete driver type, the OR increased to 8.8 and was of borderline statistical significance (95 % CI 1.0–77.8). Longo et al. (2000b) also calculated the risks associated with a group of substances acting as stimulants, including amphetamine, methamphetamine, phentermine, pseudoephedrine, ephedrine and MDEA. There was no significantly increased responsibility risk associated with driving under the influence of stimulants alone.

Conclusion

Experimental studies suggest that a dose of 25 mg of ephedrine has no significant influence on performance in healthy volunteers. A dose of 50 mg, however, can partially reverse the adverse effects of depressants such as alcohol. No epidemiological studies were found on the accident risk associated with ephedrine alone, but studies investigating the risks associated with stimulants indicate no increase in risk of responsibility for an accident.

Phentermine

Phentermine, like ephedrine, is a stimulant drug similar in structure to amphetamine. Its principal indication is as a treatment for obesity, while the primary manifestation of drug use is central stimulation (Baselt, 2001).

Acute effects

Magill et al. (2003) investigated the effects of tyrosine (150 mg/kg), phentermine (37.5 mg), caffeine (300 mg/70 kg), dextroamphetamine (20 mg) or placebo on cognitive and motor performance deficits in healthy young men during sleep deprivation. The substances were administered at 3.30 p.m. following overnight sleep deprivation. Performance decrements as a result of sleep deprivation occurred in visual scanning, running memory, logical reasoning, mathematical processing, the Stroop test, the time wall test, tracking and visual vigilance. The statistical comparisons of task performances 1.5 and 5.5 hours after drug administration with baseline performances at 1.00 p.m. showed that phentermine improved performance at both time points for all tasks that had been affected by sleep deprivation. Results with phentermine and dextroamphetamine were similar.

No recent studies were found on the effects of phentermine in subjects who are not sleep deprived, but studies that were published before 1999 indicated that phentermine has the capacity to improve cognitive and motor performance in healthy volunteers under laboratory conditions (Brauer et al., 1996; Volkerts et al., 1997).

No studies were found on the chronic effects of phentermine.

Risks

No studies were found that examined the accident risks associated with phentermine, specifically. However, two responsibility analyses were found that investigated the risk of responsibility for an accident while driving under the influence of a stimulant in general (Drummer et al., 2004; Longo et al., 2000b). Neither study found a significant association between the use of stimulants and crash responsibility.

Conclusion

Experimental studies show that a dose of 20–38 mg of phentermine can improve cognitive and psychomotor performance in volunteers following sleep deprivation. No studies were found on the chronic effects or on the accident risk associated with the use of phentermine alone, but studies investigating the risks associated with stimulants indicate no increase in the risk of responsibility for an accident.

Methylphenidate

Acute effects

Barkley et al. (2005) evaluated the effects of two single, acute doses of methylphenidate (10 and 20 mg) or a placebo on the driving performance of 53 adults with ADHD (mean age 37 years, range 18–65 years) using a virtual reality driving simulator, examiner and self-ratings of simulator performance, and a CPT to evaluate attention and inhibition. A significant beneficial effect of the high dose of medication was observed on impulsiveness on CPT, variability of steering in the standard driving course and driving speed during the obstacle course. A beneficial effect of the low dose of medication was also evident on turn-signal use during the standard driving course.

MDMA and methylphenidate significantly decreased SDLP in the road-tracking tests by about 2 cm relative to placebo on day 1 (intoxication phase) (Ramaekers et al., 2006c).

Sobanski et al. (2008) performed a study of driving behaviour and history of driving outcomes in 27 clinically referred German adults with ADHD and 27 non-ADHD control subjects. In 19 of the subjects with ADHD, a test battery of driving-related cognitive measures was performed with the standardised Act and React Test (ART) 2020 system battery and reassessed after at least 6 weeks of treatment with methylphenidate (n = 9) or after a 6-week medication-free period (n = 10). Compared with control subjects, subjects with ADHD drove significantly more kilometres per year, were more often registered by traffic authorities and fined more frequently, were involved in more accidents and described their driving style as more insecure and hectic. Methylphenidate treatment resulted in improved information processing, for example better visuomotor coordination under high-stress conditions, improved visual orientation and sustained visual attention compared with baseline and the untreated control group.

Verster and Cox (2008) performed a randomised, crossover trial examining the effects of methylphenidate versus placebo on highway driving in 18 adults with ADHD. After 3 days of no treatment, patients received either their usual methylphenidate dose (mean 14.7 mg, range 10–30 mg) or placebo and then the opposite treatment after a 6- to 7-day washout period. Patients performed a 100-km driving test during normal traffic, 1.5 hours after treatment administration. Driving performance was significantly better in the methylphenidate than in the placebo condition, as

reflected by the difference in SDLP (2.3 cm; 95 % CI 0.8–3.8). Variation in speed was similar on treatment and on placebo (–0.05 km/h, 95 % CI –0.4 to 0.2). Among adults with ADHD with a history of a positive clinical response to methylphenidate, methylphenidate significantly improved driving performance.

Cox et al. (2008) investigated whether OROS (osmotic controlled release oral delivery system) methylphenidate (Concerta) was associated with worsening of driving performance, or drug rebound, relative to placebo, 16–17 hours post ingestion. Nineteen male adolescent drivers aged 17–19 with ADHD were compared. Medication was taken at 8.00 a.m. in a randomised, double-blind, placebo-controlled, crossover study. OROS methylphenidate was not associated with significant worsening of simulator performance relative to placebo 17 hours post ingestion in group comparisons.

Cox et al. (2012) demonstrated that long-acting methylphenidate improves activities of daily living among young adults with ADHD. Specifically, methylphenidate improved safety in routine driving while reducing ADHD symptoms with minimal adverse effects.

Conclusion

Among patients with ADHD, with a history of a positive clinical response to methylphenidate, methylphenidate significantly improves driving performance.

Conclusion

According to experimental studies, most of the illicit drugs discussed in this report can affect driving performance.

Cannabis may impair some of the cognitive and psychomotor skills required to drive. Most of these effects increase in a dose-dependent way. A cannabis user is aware of the impairment, but can only partially compensate for the decrements. In an experimental fMRI study (Battistella et al., 2013), subjects were more attracted by intrapersonal stimuli ('self') and failed to attend to task performance, leading to an insufficient allocation of task-orientated resources and to suboptimal performance. Use combined with alcohol can cause additional impairment. Chronic use of cannabis can lead to deficiencies in performance that last longer than the period of intoxication and worsen with either increasing number of years or frequency of cannabis use. Meta-analyses of the data from epidemiological studies have shown that cannabis use is associated with a twofold increased risk of being involved in an accident.

Numerous studies on the opioids suggest that heroin use might lead to severe impairment, while there is much less impairment with use of methadone and little impairment with buprenorphine use; however, these results were highly dependent on the dose given and subjects' drug use history. The effects of medicinal opioids are mostly moderate. Methadone maintenance treatment does cause impairment, including additional impairment over and above that associated with heroin dependence, a finding that in some cases can be better explained by other associated risk factors. Buprenorphine users have not generally shown impairment, except at high doses. A systematic review found limited epidemiological research suggesting that opioids may be associated with increased accident risk in the first few weeks of treatment.

Stimulants have repeatedly been shown to improve neuropsychological skills, such as tracking, impulse control and reaction time, while impairing cognitive functions such as working memory and movement perception.

Driving under the influence of stimulants is generally safe when the drugs are taken alone and in regular doses (e.g. as in medicinal use), but stimulant drugs are less safe when taken in combination with sleep loss or alcohol intoxication, as is often the case in recreational drug users. The use of MDMA can diminish some, but not all, deleterious effects of alcohol, while other negative effects of alcohol can be reinforced. The stimulatory effects of dexamphetamine are not sufficient to overcome the impairing effects of alcohol or sleep deprivation on skills related to driving. There is large variation in subjects' sensitivity to combinations of amphetamine and alcohol or MDMA and alcohol; some show impairment, whereas others do not. Meta-analyses of the crash risk associated with the use of amphetamines have shown high odds ratios.

The few studies that were found on the effects of cocaine suggest that low doses appear not to affect performance or even to improve it, but chronic use causes various deficiencies in performance and an increase in compulsive behaviour. A meta-analysis showed that the relative risk of accident involvement with cocaine is 1.5 to 3.

Synthetic drugs such as GHB, ketamine and PCP (in subanaesthetic doses) can reduce cognitive and psychomotor performance. Ephedrine and phentermine

were found not to affect performance and sometimes they even improved it.

Experimental studies on the effects of consuming both alcohol and illicit drugs on performance found that the combination of some illicit drugs (e.g. cannabis) with alcohol can cause impairment in addition to that caused by either substance alone, while other illicit drugs (e.g. cocaine) may partially reverse the impairment caused by alcohol. MDMA diminishes some, but not all, deleterious effects of alcohol, while other negative effects of alcohol may be reinforced. Generally, the chronic use of illicit drugs such as cannabis, amphetamines, cocaine or heroin is associated with cognitive and/or psychomotor impairment, and may lead to impaired driving performance, even when the subject is no longer intoxicated.

One limitation to many of the experimental studies on illicit drugs is that the doses administered are not always representative of doses that might in reality be consumed by drug users. For heroin, no recent experimental studies have been conducted using realistic doses. This is also the case for studies on cocaine. In the few experimental studies that exist on the acute effects of cocaine, the study limitations include the administration of low doses and oral administration (which produces fewer effects at a slower onset).

The results of experimental studies on therapeutic drugs show obvious impairment for some, such as some of the first-generation antihistamines, benzodiazepines and TCAs. Nevertheless, in every therapeutic class, some substances have been associated with little or no impairment, and these should preferably be prescribed to drivers. Meta-analyses show that the relative risk of crashes is approximately 1.6 to 1.8 for benzodiazepines. In combination with alcohol, the relative risk increases to approximately 8.

Some benzodiazepines and related drugs should generally be regarded as unlikely to have a residual effect in the morning. These include zaleplon 10 mg, lormetazepam 1 mg and temazepam 20 mg (immediate-release capsules). It should also be noted that, with chronic and subchronic use, tolerance might develop, partially or completely, to the impairing effects that have been observed for some benzodiazepines. Based on the studies on antihistamines, it seems that bilastine, desloratadine, ebastine, fexofenadine, levoceterizine and rupatadine (which are second-generation antihistamines) are the least impairing options. Fexofenadine in particular, in contrast to the other drugs, does not potentiate the effects of alcohol or vice versa. In addition, the use of topical azelastine (second generation, class phthalazinones) does not appear to affect vigilance. In a meta-analysis the relative risk of accident involvement with antihistamines was 1.12 (95 % CI 1.02–1.22) for injury, which illustrates the low risk.

Experimental data on antidepressants show that TCAs (first generation), when compared with the more recent second-generation antidepressants, lead to greater impairment of cognition and psychomotor skills, though tolerance does seem to develop. Nevertheless, caution is advised when prescribing these older substances to drivers, since previous studies clearly demonstrate an impairing effect. As for the second generation, the results from various studies are not always consistent, partly because the drugs' effects on memory and cognition can be difficult to interpret since depression often leads to cognitive deficits. Patients obviously benefit from treatment with newer antidepressants; however, at least a subgroup does not reach the performance level of healthy subjects. In a meta-analysis the relative risk of accident involvement with antidepressants was approximately 1.30.

Combinations of therapeutic drugs also increase risk. As an illustration, the recent case–control study by Bogstrand et al. (2012) found the greatest increase in risk of injury was associated with alcohol combined with any other substance (OR 231.9; 95 % CI 33.3–1615.4), more than three psychoactive substances (OR 38.9; 95 % CI 8.2–185.0) and alcohol alone (OR 36.1; 95 % CI 13.2–98.6). The adjusted ORs were 1.4 (95 % CI 0.4–4.4) for one non-alcohol psychoactive substance, 17.1 (95 % CI 4.2–41) for two substances and 38.9 (95 % CI 8.2–185.0) for three substances.

Overall conclusion

The use of illicit drugs in the European Union as reported by the EMCDDA has, as a whole, increased since the late 1990s, but it is now stabilising. Experimental and epidemiological studies show that, while alcohol is still the number one substance endangering lives on European roads, drug and medicine use among drivers is a problem that needs to be addressed. In Europe, overall, 7.43 % of drivers studied tested positive for alcohol or one of the 23 tested drugs in their oral fluid or blood. Alcohol above 0.1 g/l was found in 3.48 % of the drivers, and above 0.5 g/l in 1.5 %. Regarding drugs, 1.9 % tested positive for illicit drugs, mainly cannabis, 1.4 % for medicinal drugs (a limited list of benzodiazepines, Z-hypnotics and opioids), 0.37 % for a combination of alcohol and drugs and 0.39 % for different drug classes. The range of psychoactive substances available for illicit use is increasing, and recent studies are finding evidence of their use among drivers. Whether drivers are tested randomly, upon suspicion, in hospital or after a fatal accident, various subsets of motorists are being found with a range of drugs in their system.

Research covered in this report can be broadly split into two types: experimental and epidemiological. Each type has its advantages and disadvantages. Experimental research consists of performance, driving simulator and/or real on-the-road tests. These studies avoid unknown external factors and allow the doses to be controlled, but often cannot simulate the doses or environment actually experienced by drug users on the roads. In contrast, the types of epidemiological studies are manifold, from daytime random roadside surveys, which may show a prevalence of 1 %, through to questionnaire surveys of young chronic drug users that may indicate a prevalence of 85 %. These results can be used to calculate the statistical risks of involvement in and responsibility for an accident. Sample sizes can be quite small for various reasons, and different study samples cannot be added for the reasons described above. Nevertheless, given the inherent characteristics of each type of study, a good estimate of the impact will be obtained by combining the results of both.

Cannabis is the most prevalent illicit drug detected in drivers and benzodiazepines are the most prevalent therapeutic drug group. In studies that tested for both among drivers involved in accidents (fatal or non-fatal), benzodiazepines were sometimes even more prevalent than cannabis. However, when drivers were tested only on suspicion, cannabis was the most prevalent drug.

Most illicit drugs can have an effect on varying aspects of driving performance. Some dose- or concentration-dependent impairment has been shown, but for only a few substances, so increased effects at higher doses, or diminished effects at lower doses, should not always be assumed. Cannabis, GHB, ketamine and PCP can reduce cognitive and psychomotor performance, while low doses of amphetamine or methamphetamine may improve cognitive and psychomotor performance but could also reduce driving capacity during the day as a result of tunnel vision. Experimental studies with low or medium doses of MDMA showed no impairment of, or even improvement in, psychomotor function, but some decrease in memory functions. Similarly, of the few studies on cocaine since 1999, low doses appear not to affect performance and may even improve it, but chronic use causes various deficiencies in performance and an increase in compulsive behaviour. Numerous studies on opioids suggest the possibility of severe impairment with heroin use, while those in substitution treatment programmes experience much less impairment with methadone and little with buprenorphine use; however, it should be kept in mind that these results were highly dependent on the dose given and type of subjects tested, as well as their history.

Other therapeutic substances also showed considerable differences in the effects by group. Benzodiazepines generally have impairing effects, with some types (whether long-,

medium- or short-acting) causing severe impairment and others unlikely to have residual effects in the morning. First-generation antihistamines are generally more sedating than second-generation ones, though there are exceptions in both groups. TCAs cause more impairment than the more recent types, though the results of experimental studies on the effects of SSRIs are not always consistent. In every therapeutic class, some substances have been associated with little or no impairment, and it should preferably be these that are prescribed to patients who wish to drive. With most medicinal drugs, tolerance also has a significant effect, as does the indication that is being treated (such as pain or depression). However, in some cases, although a drug may cause measurable impairment of some functions, it may nevertheless improve the patient's overall ability to drive.

Based on the results of meta-analyses, it is possible to establish the increased risk of several drug classes (Figure 4). The odds ratios for the major drug classes, based on different meta-analyses, are given in Table 11.

Figure 4 illustrates the 'position' of each substance with respect to prevalence and injury risk. The three substance categories that are connected with extreme high risks (OR > 10) are the two high alcohol concentrations (0.8–1.2 and > 1.2 g/l) and the combination of alcohol and drugs, all of them presenting with moderate prevalence rates of about 0.4 %. Associated with a 5- to 10-fold increased risk of injury are the amphetamines, medicinal opioids and drug–drug combinations, but prevalence rates are much lower (0.08 % for amphetamines), and therefore there is less demand for action. Use of illicit opioids, Z-hypnotics and cocaine increases the relative risk of injury by a factor of between 2 and 3 and prevalence rates are below 0.5 %. Alcohol at concentrations between 0.5 and 0.8 g/l, benzodiazepines and THC show all prevalence rates higher than 0.5 %, which would call for action from this point of view. However, the epidemiological risks associated with benzodiazepines (OR 3) and THC (OR 2) are smaller than the risk associated with alcohol concentrations that are comparable to the legal limit in most European countries. Additionally, it is important to remember that the benzodiazepines group comprises a huge

FIGURE 4

Plot of the prevalence of driving under the influence of different drugs and the accident risk (after Hargutt, 2011).

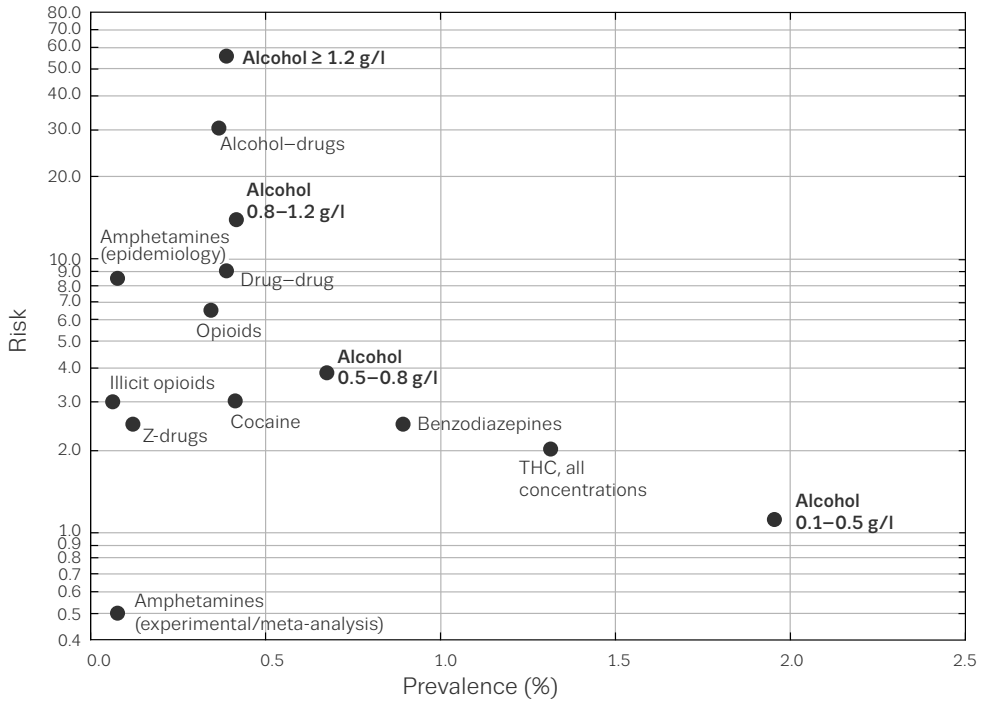


TABLE 11

Typical odds ratios for injury or death as a result of a car crash while under the influence of alcohol, medicinal or recreational drugs, based on meta-analyses and DRUID case–control studies

	Odds ratio (95 % CI)	Reference
Alcohol 0–0.49 g/l	1.18 (0.81–1.73)	Hels et al. (2011)
Alcohol 0.5–0.79 g/l	**3.64 (2.31–5.72)**	Hels et al. (2011)
Alcohol 0.8–1.2 g/l	**13.35 (8.15–21.88)**	Hels et al. (2011)
Alcohol ≥ 1.2 g/l	**62.79 (44.51–88.58)**	Hels et al. (2011)
Amphetamines	**6.19 (3.46–11.06)**	Elvik (2013) (1)
Antidepressants	**1.32 (1.08–1.70)**	Elvik (2013) (1)
Antihistamines	**1.12 (1.02–1.22)**	Elvik (2013) (1)
Benzodiazepines	**1.59 (1.10–2.31)**	Dassanayake et al. (2011)
Cannabis	**1.92 (1.35–2.73)**	Asbridge et al. (2012)
Cocaine	1.66 (0.91–3.02)	Elvik (2013) (1)
Opioids	**1.89 (1.47–2.43)**	Elvik (2013) (1)

(1) As odds ratios are given for different crashes, we give the odds ratio for injury crashes here.
NB: Significantly increased odds ratios are shown in bold.

number of substances that result in very different impairment levels depending on their concentration. Last, but not least, no elevated risk could be proved for low alcohol concentrations (0.1–0.5 g/l) and amphetamines, as shown in the experimental studies and the meta-analysis.

Some of the conclusions from the DRUID project (Hargutt et al., 2011), from the perspective of traffic safety, especially looking at prevalence rates and risks, were as follows. Alcohol, especially in high concentrations, must remain focus number one. The combination of alcohol and drugs or medicines seems to be a topic that should be addressed more intensively because it leads to very high risks in traffic. The problems of medicine use among drivers should be addressed by providing doctors and patients with relevant information, rather than by defining thresholds. THC and amphetamines are a minor risk based on experimental studies, but the OR for amphetamines is high in case–control studies. More research is needed to investigate probable risks of amphetamines in real traffic and the mediating factors. From the perspective of risk, sleep deprivation should also be addressed as a high accident risk factor.

This report aims to add to the knowledge accumulated in the 1999 and 2008 literature reviews (EMCDDA, 1999, 2008), but it bears repeating that, while the EMCDDA strives for comparable statistics on the drug situation in Europe, there is no indication of the comparability of the statistics analysed here. To give a simple example, cases 'positive' for a drug registered at above 1 ng/ml cannot be equated with 'positives' registered at above 3 ng/ml. To obtain more compatible methodologies, in 2006–07 a committee of international experts, including representatives from the EMCDDA and National Institute on Drug Abuse, drafted guidelines for future research into drugs and driving (Walsh et al., 2008). According to these guidelines, comparisons of such cases should take into account the different study designs, biological matrices tested, cut-off levels and so on. The DRUID project took account of these guidelines but, based on the findings of this project, more widespread implementation of the guidelines is required.

Prevention programmes that address drugs and driving are in place in the form of training in driving schools as well as various public safety campaigns, though these may not always be effectively targeted. In prescribing psychoactive medications, whether for traditional pain management, antidepressant use or substitution treatment, the challenge is to prescribe a dose that is high enough to have the desired therapeutic effect but not enough

to cause loss of driving skills or ability, something that could seriously affect the patient's quality of life. There remain concerns about the accuracy of roadside detection mechanisms, whether traffic police with special training or testing of drivers' biological samples, although considerable progress has been observed very recently.

To deliver a clear public message, both scientists and policymakers must attempt to define, for each drug, a cut-off blood concentration above which performance is impaired, similar to the commonly understood BAC. This would give a simple legal threshold to indicate at what stage impairment becomes dangerous for users or for those around them. Yet, although the BAC figure has become generally accepted after decades of research, Member States have resisted attempts by the European Union to harmonise it (similarly, they are still sharply divided on the issue of testing at random or only on suspicion, even for excess alcohol).

In addition, it is difficult to implement a threshold analogous to BAC for other psychoactive substances because of the vastly different pharmacological natures of the range of substances involved, the limitations of experimental and epidemiological research in trying to determine any such cut-off level, the ethical considerations involved in its enforcement and the question of combining or separating drug abuse control and road safety measures. Specifically, it is unacceptable to some that a driver be punished for driving with an amount of drug that has no relevant effect on driving, while it is equally unacceptable to others to condone illicit drug use by stating that, up to a certain threshold, it will not be punished. This can be seen in the various country legislations, some of which will use a positive blood sample to convict only for a driving offence, while others will use that sample, taken for proving a driving offence, to prosecute for a drug use offence. On top of all this complexity comes the finding that a considerable number of drivers have been found to have multiple drugs, including alcohol, in their blood, some combinations of which have been proven to have synergistic effects. In Norway, where limits for graded sanctions have been implemented, and in the Netherlands, cut-off levels based on equivalence to a BAC of 0.5 g/l are under consideration.

Studying the relationships between drug use, impaired driving and traffic accidents is a remarkably complex subject, and this simple review does not pretend to give any definitive solutions; as with many research projects, sometimes the answers found merely give rise to more questions. Nevertheless, the EMCDDA, particularly now that the data from the DRUID project are available, aims to give a more accurate delimitation of the problem to date in this fast-moving area of research to assist policymakers in choosing more effective solutions for their countries.

Abbreviations

11-OH-THC	11-hydroxy-Δ^9-tetrahydrocannabinol
ADHD	attention-deficit hyperactivity disorder
ATC	Anatomical Therapeutic Chemical
BAC	blood alcohol concentration
BRT	brake reaction time
BVRT	Benton visual retention test
CFF	critical flicker fusion
CI	confidence interval
CLT	circular lights task
CNS	central nervous system
CPT	continuous performance test
CRT	choice reaction time
CTT	critical tracking test
DRUID	Driving under the Influence of Drugs, Alcohol and Medicines
DSST	digit symbol substitution test
EEG	electroencephalography
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
fMRI	functional magnetic resonance imaging
FTT	finger-tapping test
GABA	gamma-aminobutyric acid
GHB	gamma-hydroxybutyrate
Immortal	Impaired Motorists, Methods of Roadside Testing and Assessment for Licensing
LARS	line analogue rating scale
LMT	learning memory task
MBDB	*N*-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine
MDA	3,4-methylenedioxyamphetamine
MDEA	3,4-methylenedioxyethylamphetamine
MDMA	3,4-methylenedioxymethylamphetamine
MMSE	mini-mental state examination
MRT	motor reaction time
MVA	motor vehicle accident
OR	odds ratio
PASAT	paced auditory serial addition task
PET	positron emission tomography
QIE	quasi-induced exposure
RR	relative risk
RRT	recognition reaction time
RVIPT	rapid visual information processing task
SAM	Stupéfiants et Accidents Mortels/illicit drugs and fatal crashes
SDLP	standard deviation of lateral position
SFST	standard field sobriety test
SIR	standardised incidence ratio
SNRI	serotonin–norepinephrine reuptake inhibitor
SRT	simple reaction time
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
THC	Δ^9-tetrahydrocannabinol
THC-COOH	11-nor-Δ^9-THC-9-carboxylic acid
TMT	trail-making test
TRT	total reaction time
WAIS	Wechsler adult intelligence scale
WCST	Wisconsin card sorting test

Appendix

Appendix

TABLE A1

Results of the roadside surveys performed during the DRUID project (percentage prevalence and confidence intervals)

	Negative	Amphe-tamines	Cocaine	THC	Illicit opioids	Benzodia-zepines	Z–hypnotics	Medicinal opioids	Alcohol	Alcohol + drugs	Drugs–drugs
Belgium	89.35 *88.18–90.41*	– –	0.2 *0.09–0.43*	0.35 *0.19–0.64*	0.09 *0.03–0.28*	2.01 *1.57–2.59*	0.22 *0.1–0.47*	0.75 *0.5–1.13*	6.42 *5.59–7.36*	0.31 *0.16–0.58*	0.3 *0.16–0.58*
Czech Republic	97.2 *96.39–97.83*	0.36 *0.17–0.72*	– –	0.46 *0.25–0.86*	– –	0.62 *0.36–1.07*	– –	0.21 *0.08–0.52*	0.99 *0.65–1.53*	0.05 *0.01–0.28*	0.11 *0.03–0.38*
Denmark	95.52 *94.72–96.2*	0.02 *0–0.16*	– –	0.2 *0.09–0.43*	– –	0.47 *0.28–0.79*	0.32 *0.17–0.59*	0.79 *0.53–1.18*	2.53 *2.02–3.15*	0.1 *0.03–0.3*	0.06 *0.02–0.24*
Finland	97.15 *96.58–97.63*	0.05 *0.02–0.19*	0.03 *0.01–0.16*	0.04 *0.01–0.17*	– –	0.79 *0.56–1.13*	0.36 *0.21–0.6*	0.56 *0.37–0.85*	0.64 *0.43–0.94*	0.08 *0.03–0.23*	0.29 *0.16–0.52*
Hungary	97.68 *97.04–98.18*	– –	0.04 *0.01–0.21*	0.19 *0.08–0.44*	– –	1.5 *1.11–2.03*	0.07 *0.02–0.26*	0.11 *0.04–0.32*	0.15 *0.06–0.38*	– –	0.27 *0.13–0.54*
Italy	84.99 *82.95–86.82*	– –	1.25 *0.78–2.01*	1.15 *0.7–1.89*	0.3 *0.12–0.78*	0.97 *0.57–1.67*	– –	0.53 *0.25–1.09*	8.59 *7.19–10.23*	1.01 *0.59–1.71*	1.22 *0.75–1.97*
Lithuania	94.49 *93.09–95.61*	0.22 *0.07–0.66*	– –	– –	– –	1.41 *0.9–2.23*	– –	– –	3.86 *2.93–5.06*	0.03 *0–0.36*	– –
Netherlands	94.49 *93.81–95.1*	0.19 *0.1–0.36*	0.3 *0.18–0.5*	1.67 *1.34–2.07*	0.01 *0–0.09*	0.4 *0.25–0.62*	0.04 *0.01–0.15*	0.16 *0.08–0.32*	2.15 *1.78–2.6*	0.24 *0.13–0.42*	0.35 *0.22–0.56*
Norway	97.03 *96.67–97.36*	0.06 *0.02–0.13*	0.06 *0.03–0.14*	0.48 *0.36–0.64*	– –	0.84 *0.67–1.05*	0.69 *0.54–0.88*	0.16 *0.1–0.27*	0.32 *0.23–0.46*	0.07 *0.03–0.15*	0.28 *0.19–0.42*
Poland	97.63 *97.11–98.05*	0.05 *0.01–0.18*	– –	0.57 *0.38–0.85*	0.09 *0.04–0.25*	0.14 *0.06–0.31*	– –	0.03 *0.01–0.15*	1.47 *1.14–1.9*	– –	0.02 *0–0.14*
Portugal	90.01 *89.04–90.91*	– –	0.03 *0.01–0.16*	1.38 *1.07–1.8*	0.15 *0.07–0.33*	2.73 *2.27–3.29*	– –	0.11 *0.04–0.27*	4.93 *4.29–5.64*	0.42 *0.26–0.67*	0.23 *0.12–0.44*
Spain	85.15 *83.87–86.34*	0.11 *0.04–0.3*	1.49 *1.12–1.97*	5.99 *5.22–6.87*	0.05 *0.01–0.2*	1.4 *1.05–1.87*	– –	0.19 *0.09–0.41*	3.92 *3.3–4.66*	1.14 *0.83–1.58*	0.57 *0.36–0.89*
Sweden	98.66 *98.34–98.92*	0.07 *0.03–0.17*	– –	0.03 *0.01–0.12*	– –	0.19 *0.11–0.33*	0.31 *0.2–0.48*	0.63 *0.46–0.86*	– –	– –	0.12 *0.06–0.25*

NB: Values given for a drug class refer to the presence of that class of drugs alone; data for drugs found in combination with alcohol or combinations of more than one class of drugs are given in the two last columns.

TABLE A2
Results of the roadside surveys in other countries (percentage of drivers in whom the drugs were detected)

	Australia	Brazil	Canada (British Columbia)	China	Norway		Thailand	United States (California)	United States	United States
Study	**Davey and Freeman (2009)**	**Leyton et al. (2012)**	**Beasley and Beirness (2012)**	**Zhuo et al. (2010)**	**Gjerde et al. (2008)**	**Gjerde et al. (2012)**	**Ingsathit et al. (2009)**	**Johnson et al. (2012)**	**Lacey et al. (2011)**	**Lacey et al. (2011)**
Year(s)		2009	2012	2007–8	2005–6	2008–9	2005–6	2010	2007	2007
Sample size	1 587	456	1 757	10 002	10 816	882	1 635	900	1 850	5 910
Biological sample	Oral fluid	Urine	Breath and oral fluid	Blood	Oral fluid	Oral fluid	Urine (drugs), breath (alcohol)	Oral fluid	Oral fluid	Blood or oral fluid
Remark		Truck drivers	Only night-time, Wednesday to Saturday	Drivers involved in traffic accident or violation		Only truck drivers		Only weekend night-time drivers	Daytime	Night-time
Positive (%)	3.7		12.0		4.5	1.9				
Weighted	No	No	Yes		Yes	No		No	Yes	Yes
Alcohol detected (%)			8.3		0.4	0.1				
> 0.1 g/l (%)			8.3		0.4	0.1			1.0	12.4
> 0.2 g/l (%)							5.5			
> 0.5 g/l (%)			3.0						0.1	4.5
> 0.8 g/l (%)	3.7		1.6						0.1	2.2
Drugs (illicit and medicinal) (%)		9.3	10.1	10.5		1.9	9.7		11.0	16.3
Illicit drugs (%)				0.26	1.0	1.1	2.3	14.4		
Medicinal drugs (%)	3.7				3.4	0.8	6.3			
Drugs + alcohol detected (%)			0.6		0.1			1.3		3.4
Different drug classes (%)		0.2	1.7		0.6				1.5	2.3
Amphetamine (%)		5.8	1.4		0.29	0.1	1.8		0.56	0.45
Methamphetamine (%)	1.1	0.0		0.15	0.12	0.1			0.56	0.84
MDMA (%)	2.3			0.01		0.0			0.06	0.09
Cocaine (%)	0.1	2.2	3.3		0.04	0.3			1.46	3.9
Cannabis (%)	1.3	1.1	4.4		0.6	0.7	1.1	8.5	4.46	8.6
Benzodiazepines (%)			0.05	0.46	1.4 Zolpidem: 0.02 Zopiclone: 1.42	Alprazolam: 0.1 Desmethyldiazepam: 0.5 Zopiclone: 0.1	0.2		1.6	Alprazolam: 0.64 Diazepam: 0.38 Clonazepam: 0.14

	Australia	Brazil	Canada (British Columbia)	China	Norway		Thailand	United States (California)	United States	United States
Study	**Davey and Freeman (2009)**	**Leyton et al. (2012)**	**Beasley and Beirness (2012)**	**Zhuo et al. (2010)**	**Gjerde et al. (2008)**	**Gjerde et al. (2012)**	**Ingsathit et al. (2009)**	**Johnson et al. (2012)**	**Lacey et al. (2011)**	**Lacey et al. (2011)**
Opioids (%)			0.9	0.11 Tramadol: 0.05 Oxycodone: 0.07	Codeine: 0.8 Morphine: 0.08 Buprenorphine: 0.02	Codeine: 0.2	Morphine: 0.1		1.6	Oxycodone: 0.82 Hydrocodone: 0.68 Propoxyphene: 0.52 Codeine: 0.44
Antihistamines (%)							2.0			
Methadone (%)					0.03	0.0			0.21	0.19
Barbiturates (%)									0.26	0.18
TCA (%)									0.5	0.97
Ketamine (%)				0.03					0.00	0.08

Abbreviations: MDMA, 3,4-methylenedioxymethylamphetamine; TCA, tricyclic antidepressant.

TABLE A3

Results of the DRUID studies in injured drivers (percentage of the drivers in whom the drugs were detected)

	Belgium	Denmark	Finland	Italy	Lithuania	Netherlands
Positive drivers	52.6	30.3	44.7	32.0	27.8	33.9
Female Male	37.2 59.1	15.8 38.1	20.0 51.4	23.7 34.4	20.9 32.4	13.5 38.9
Alcohol						
≥ 0.1 g/l	42.5	19.7	32.1	23.1	17.7	29.6
0.1 g/l ≤ alcohol ≤ 0.5 g/l	4.3	1.9	1.9	2.5	1.6	1.6
≥ 0.5 g/l	38.2	17.8	30.2	20.6	16.1	28.0
Amphetamines Alone	2.6 0.9	4.2 1.0	3.7 0.0	0.1 0.0	0.6 0.3	2.2 1.1
Cocaine Alone	2.3 0.0	0.6 0.0	0.0	2.7 0.6	0.3 0.3	2.1 0.0
Tetrahydrocannabinol Alone	7.6 1.5	1.3 0.6	5.7 1.9	3.7 1.6	0.5 0.3	0.5 0.5
Illicit opioids Alone	0.6 0.0	0.5 0.0	0.0	2.1 0.7	0.3 0.0	0.0
Benzodiazepines Alone	7.3 1.5	6.7 1.2	10.2 0.0	0.7 0.4	3.6 2.3	0.0
Z-hypnotics Alone	1.8 0.9	1.2 0.5	3.8 1.9	0.0	0.0	0.5 0.5
Medicinal opioids Alone	3.3 1.8	4.2 2.5	4.0 2.0	3.7 1.8	7.8 5.7	0.5 0.5
Alcohol–drug combination	13.2	5.4	10.6	4.6	2.3	4.3
Drug–drug combination	2.5	3.5	4.3	2.5	0.8	0.5

TABLE A4

Results of the studies of injured drivers surveys that are not part of the DRUID project (percentage of the drivers in whom the drugs were detected)

	Australia		Brazil		Greece	Hong Kong	Italy		Netherlands	Norway	Spain	Sweden
Study	**Drummer et al. (2012)**	**Ch'ng et al. (2007)**	**De Boni et al. (2011)**	**Breitenbach et al. (2012)**	**Papadodima et al. (2008)**	**Wong et al. (2010)**	**Ricci et al. (2008)**	**Siliquini et al. (2007)**	**Smink et al. (2008b)**	**Bogstrand et al. (2011)**	**Santamarina-Rubio et al. (2009)**	**Ahlm et al. (2009)**
Year(s)	2009	2000–2	2008	2008	1998–2004	2007	2006	2005	2000–1	2007–8	2005–6	2005–7
Sample size	1 717	436	361	283	3 167	395	100	200	106	1 272	272	144
Sample	Blood	Blood	Saliva	Saliva	Drugs in urine Alcohol in blood	Urine	Drugs in urine Alcohol in blood	Urine		Blood	Saliva	Blood
Remark				Only motorcycle drivers			Drivers of cars, bicycles and motorcycles, passengers and pedestrians	Weekend only	Only car and van drivers	Data from patients with injuries from accidents, assaults or deliberate self-harm	Data from drivers, passengers and pedestrians. Only data from drivers are reported	Killed and injured drivers; only data of injured drivers are reported
Positive (%)					37	10	43	18.5	43	44	M: 32.4 F: 16.1	31
Alcohol detected (%)			7.8	7	29						M: 16.8 F: 9.9	20.8
> 0.1 g/l (%)	29.0						31			26.8		
> 0.2 g/l (%)												
> 0.5 g/l (%)					37							
Drugs (illicit and medicinal) (%)	35.0	9.4			9	3.0			23			
Illicit drugs (%)	12.5						10			9	M: 17.9 F: 5.9	4
Medicinal drugs (%)										21		13
Drugs + alcohol detected (%)	12.0				2.2	7						7
> 0.2 ‰ (%)							14					
> 0.5 ‰ (%)												
Drug + drug (%)		9.4				3.0		5.5				
Amphetamine (%)		4.1				0.25	10	0	7	2.5		
Methamphetamine (%)	3.1					6	0	0		2.5		
MDMA (%)	0.8						1	0		0.2	M: 1.1 F: 0.0	
Cocaine (%)	0.0	1.4	8.4	9.2	1	1.3	7	9.5	9	1.6	M: 7.1 F: 3.6	

TABLE A4 (continued)

	Australia		Brazil		Greece	Hong Kong	Italy		Netherlands	Norway	Spain	Sweden
Study	**Drummer et al. (2012)**	**Ch'ng et al. (2007)**	**De Boni et al. (2011)**	**Breitenbach et al. (2012)**	**Papadodima et al. (2008)**	**Wong et al. (2010)**	**Ricci et al. (2008)**	**Siliquini et al. (2007)**	**Smink et al. (2008b)**	**Bogstrand et al. (2011)**	**Santamarina-Rubio et al. (2009)**	**Ahlm et al. (2009)**
Cannabis (%)	9.8	THC: 7.6 THC–COOH: 46.7	13.3	15.3	4	1.5	12	3.5	12	6.2	M: 16.3 F: 2.4	4.2
Benzodiazepines (%)	8.9	11		3.2	4	2.3	18	7.5	10	11.6	M: 1.1 F: 1.2	6.3
Opioids (%)	9.4				4	Morphine: 3.0	6	Morphine: 3.5	8	Codeine: 3.9 Morphine: 2.0 Buprenorphine: 0.2	M: 0.0 F: 0.0	5.6
Antihistamines (%)												
Methadone (%)	1.1	3.0				0.25	1	3.5	1	0.7		
Barbiturates (%)						0.25	0		2	0.2		
Antidepressants (%)	9.2						5	0	1			4.9
Ketamine (%)						4.3						

Abbreviations: F, female; M, male; MDMA, 3,4-methylenedioxymethylamphetamine.

TABLE A5

Overview of the results in killed drivers in DRUID (percentage of the drivers in whom the drugs were detected)

		Finland	Norway	Portugal	Sweden	Total
Total number		483	193	285	157	1 118
Positive for any substance (%)		42.3	40.0	47.7	30.5	41.8
Alcohol (≥ 0.1 g/l) (%)	Prevalence Alone	31.4 24.4	25.4 18.6	44.9 38.9	19.0 15.1	32.1 25.9
	Median BAC	1.8	1.1	1.4	1.5	1.6
Amphetamines (%)	Prevalence Alone	2.1 0.6	7.4 1.1	0.0 0.0	6.6 2.7	3.1 0.8
Cocaine (%)	Prevalence Alone	0.0 0.0	0.0 0.0	0.7 0.0	0.7 0.0	0.3 0.3
Tetrahydrocannabinol (%)	Prevalence Alone	1.3 0.0	6.1 1.7	0.0 0.0	1.3 0.7	1.8 0.4
Illicit opioids (%)	Prevalence	0.0	0.0	0.0	0.0	0.0
Benzodiazepines (%)	Prevalence Alone	13.3 5.4	9.7 1.7	1.8 0.7	3.9 0.0	8.3 2.8
Z-hypnotics (%)	Prevalence Alone	3.0 1.7	4.4 1.6	0.0 0.0	3.2 2.6	2.5 1.4
Medicinal opioids (%)	Prevalence Alone	2.1 1.5	1.7 0.6	2.1 0.7	4.1 1.4	2.3 1.1

Abbreviation: BAC, blood alcohol concentration.

TABLE A6
Overview of the prevalence of alcohol and drugs in killed drivers in other studies (percentage of the drivers in whom the drugs were detected)

	Canada	France	Nordic countries	Norway	Portugal	Sweden		United Kingdom	United States
Study	**Beasley et al. (2011)**	**Biecheler et al. (2008)**	**Morland et al. (2011)**	**Gjerde et al. (2011)**	**Costa et al. (2012)**	**Ahlm et al. (2009)**	**Jones et al. (2009)**	**Brady and Li (2013)**	**Elliott et al. (2009)**
Year(s)	2000–7	2001–3	2000–2	2006–8	1990–2007	2005–7	2003–7	2005–9	2000–6
Sample size	5 929	10 682	1 285	196	Drugs analysed in 137 cases, ethanol in 1 687	56	1 403	20 150	1 047
Sample	Coroners' data		Blood	Blood		Blood	Blood and urine	Blood and/or urine	Blood and urine
Remark		All drivers involved in a fatal accident		Only drivers of cars and vans	Prevalence determined in road traffic victims (not only drivers)	Study with killed and injured drivers; only data of killed drivers are reported			Study included various victim groups. Only data from drivers presented (n = 603)
Positive (%)	55	26	42	37.8			40.0	57.3	54.0
Alcohol detected (%)	37		27.3	25.0	31.0	38.0		40.2	42.0
> 0.1 ‰ (%)									
> 0.2 ‰ (%)							22.0		
> 0.5 ‰ (%)		21							
> 1.2 ‰ (%)					54.1				
Drugs (illicit and medicinal) (%)	33		25	6.1			18.0		32.0
Illicit drugs (%)		8.2		10.2	9.5	11.0	4.8		
Medicinal drugs (%)				13.8		7.0	15.3		
Drugs + alcohol detected (%)		3.0		5.1			5.2	19.9	26.0
> 0.2 ‰ (%)									
> 0.5 ‰ (%)									
Drug + drug (%)									
Amphetamine (%)	12.4	0.6	5.6	4.6		1.8	2.8	9.0	9.0
Methamphetamine (%)				4.6					
MDMA (%)				1.0					
Cocaine (%)		0.3	0.5	0.0	4.4				15.0
Cannabis (%)	16.6	6.8	4.8	4.6	2.2	5.4		10.5	35.0
Benzodiazepines (%)	17.3 (depressants)		9.9	12.3		5.4			9.0

	Canada	France	Nordic countries	Norway	Portugal	Sweden		United Kingdom	United States
Study	**Beasley et al. (2011)**	**Biecheler et al. (2008)**	**Morland et al. (2011)**	**Gjerde et al. (2011)**	**Costa et al. (2012)**	**Ahlm et al. (2009)**	**Jones et al. (2009)**	**Brady and Li (2013)**	**Elliott et al. (2009)**
Opioids (%)	6.4	1.5	Morphine: 0.4 Codeine: 0.6 Oxycodone: 0.2	Morphine: 1.0 Buprenorphine: 0.5	5.8	5.4	4.9	5.7	10.0
Antihistamines (%)			0.2						
Antidepressants (%)			5.2			5.4	6.6	4.0	18.0
Methadone (%)			2.0	0.0					
Barbiturates (%)									
Ketamine (%)									

Abbreviation: MDMA, 3,4-methylenedioxymethylamphetamine.

TABLE A7

Overview of the studies in drivers suspected of driving under the influence of drugs and alcohol (percentage of drivers in whom the substances were detected)

	Australia	Austria	Canada	Denmark	Hungary	Sweden	Switzerland
Study	**Chu et al. (2012)**	**Keller et al. (2009)**	**Palmentier et al. (2009)**	**Steentoft et al. (2010)**	**Toth et al. (2009)**	**Holmgren et al. (2007)**	**Senna et al. (2010)**
Year(s)	2009–10	2003–7	2001–5	1997–2006	2000–7	2001–4	2005
Sample size	853	1 167	733	2 340	1 740	22 777	4 794
Sample	Oral fluid	Blood	Blood	Blood	Urine/blood	Blood or urine	Blood
Remark			Analysed for alcohol: 704 Analysed for drugs: 42				
Positive (%)	96			87 (80–92)		80–85 in blood samples	89
Alcohol detected (%)		30					35
> 0.1 ‰ (%)							
> 0.2 ‰ (%)							
> 0.5 ‰ (%)				18 (9–26)			
> 0.8 ‰ (%)			90.9				
Drugs (illicit and medicinal) (%)			81		In urine: 74.3 In blood: 18.3		
Illicit drugs (%)							
Medicinal drugs (%)							
Drugs + alcohol detected (%)		23					
> 0.2 ‰ (%)							
> 0.5 ‰ (%)							
Drug + drug (%)							
Amphetamine (%)		18		13 (6–20)	In urine: 4–34 In blood: 16–48	70 Alone: 27	
Methamphetamine (%)	77				In urine: 6–43 In blood: 4–66		7
MDMA (%)	17		4.8	3 (0–8)			
Cocaine (%)	8.0	15	19.0	12 (6–18)	In urine: 9–14 In blood: 1–26	1.2	25
Cannabis (%)	42	50	42.9	27 (17–38)	In urine: 56–69 In blood: 7–90	10.7 Alone: 4.5	48
Benzodiazepines (%)	8.0	20	28.8	41(29–55)	In urine: 1.5–6 In blood: 2–9	8–10 Alone: 2.6–3.0	6
Opioids (%)	14 Codeine: 9.1 Morphine 7.7	20	Morphine: 14.3	Morphine 13 (7–20)	In urine: 10–15 In blood: 3–17	2.3–4.0 Alone: 1.4–2.1 Codeine/ morphine	10
Antihistamines (%)							
Methadone (%)	3.3		2.4	15 (9–21)	In urine: 1–4		5
Barbiturates (%)							
Tricyclic antidepressants (%)				3–4			
Ketamine (%)	1.5						

Abbreviation: MDMA, 3,4-methylenedioxymethylamphetamine.

TABLE A8

Results of experimental studies on benzodiazepines

Substance	Study	Tests	Doses	Effect
Zaleplon **Zolpidem**	Danjou et al. (1999)	CRT, DSST, CFF	Zaleplon: 10 mg Zolpidem: 10 mg	Zolpidem effects visible next morning
Zaleplon **Zolpidem** **Triazolam**	Troy et al. (2000)	Memory Learning	Zaleplon: 10 or 20 mg Zolpidem: 10 or 20 mg Triazolam: 0.25 mg	Cognitive impairment with zolpidem and triazolam 8.25 hours after administration
Zolpidem **Zaleplon**	Hindmarch et al. (2001a)	CFF CRT DSST	Zolpidem: 10 mg Zaleplon: 10 or 20 mg	Zolpidem had more residual effects than zaleplon 20 mg
Zolpidem **Zaleplon**	Verster et al. (2002a)	Memory Psychomotor performance	Zolpidem: 10 or 20 mg Zaleplon: 10 or 20 mg	Zolpidem affected performance in a dose-dependent manner
Zaleplon **Zolpidem**	Stillwell (2003) Logan and Couper (2001)	Driving cases		Driving impairment
Triazolam **Amphetamine**	Mintzer and Griffiths (2007)	Memory tasks	Triazolam: 0.25 or 0.5 mg/70 kg Amphetamine: 20 or 30 mg/70 kg	Amphetamine did not reverse effects of triazolam
Zaleplon review	Patat et al. (2001)		10 or 20 mg	No effect with zaleplon 10 mg
Triazolam **Zolpidem**	Mintzer and Griffiths (1999)	Memory	Triazolam: 0.125, 0.25 or 0.5 mg/70 kg Zolpidem: 5, 10 or 20 mg/70 kg	Impairment for triazolam
Triazolam	Greenblatt et al. (2005)	DSST–EEG correlation	0.375 mg	High degree of correlation
Zaleplon **Zopiclone** **Alcohol**	Vermeeren et al. (2002a)	Highway driving test	Zaleplon: 10 mg Zopiclone: 7.5 mg BAC: 0.3 g/l	No impairment for zaleplon
Zopiclone **Zolpidem** **Flunitrazepam**	Bocca et al. (2011)	SDLP	Zopiclone: 7.5 mg Zolpidem: 10 mg Flunitrazepam: 1 mg	Impaired
Zopiclone	Gustavsen et al. (2009)	Automotive and control behaviour		Impairment started at 16 µg/l
Temazepam **Zopiclone**	Leufkens and Vermeeren (2009)	SDLP Residual effects	Temazepam: 20 mg Zopiclone: 7.5 mg	Zopiclone impaired until 11 hours after administration in elderly drivers
Zopiclone	Mets et al. (2011)	SDLP Residual effects	7.5 mg	Performance impaired on the morning after administration
Zopiclone	Ramaekers et al. (2011)	SDLP Residual effects	7.5 mg	SDLP increased
Review of eight studies **Zopiclone**	Verster et al. (2011)	SDLP Residual effects	Zopiclone 7.5 mg	SDLP increased
Zolpidem **Flurazepam** **Ramelteon** **Lormetazepam** **Zaleplon** **Zopiclone**	Verster and Roth (2012)	Gender differences in residual effects	Zolpidem: 10 mg Flurazepam: 30 mg Ramelteon: 8 mg Lormetazepam: 1 or 2 mg Zaleplon: 10 or 20 mg Zopiclone: 7.5 mg	Gender differences for flurazepam and zolpidem
Alprazolam **Dextroamphetamine**	Mills et al. (2001)		Alprazolam: 0.5 mg Dextroamphetamine: 10 mg	Alprazolam impaired performance; dextroamphetamine enhanced performance, except with fatigue
Alprazolam	Verster et al. (2002b)	SDLP	1 mg	Serious driving impairment

TABLE A8 (continued)

Substance	Study	Tests	Doses	Effect
Alprazolam	Verster and Volkerts (2004a)	Memory		Dose-dependent impairment
Alprazolam extended release	Leufkens et al. (2007)	Standardised driving test Memory Psychomotor tests	1 mg	Severe driving impairment
Alprazolam	Bentué-Ferrer et al. (2001)	Behaviour	0.005 mg/kg	Stimulatory effect
Alprazolam	Snyder et al. (2005)	Attention Psychomotor function	0.5 or 1 mg	0.5 mg reduced attention; 1 mg reduced psychomotor performance and attention
Alprazolam Zopiclone Zolpidem	Schulze and Schumacher (2012)		Alprazolam: 0.5 mg Zopiclone: 7.5 mg Zolpidem: 10 mg	Significant driving impairment in patients and controls. Zolpidem significantly impaired driving among elderly subjects
Lorazepam Ritanserin	Van Laar et al. (2001)	SDLP	Lorazepam: 1.5 mg twice daily Ritanserin: 5 mg	Lorazepam showed marked driving impairment
Lorazepam	Matthews et al. (2002)	Memory	2.5 mg	Impairment in learning behavioural strategies
Lorazepam	Izaute and Bacon (2006)	Memory	0.038 mg/kg	Impairment
Lorazepam	Clarkson et al. (2004)	Driving cases		Driving impairment
Lorazepam Alcohol	Soo-ampon et al. (2004)	Recall memory	Lorazepam: 2 mg BAC: 0.6 g/l	Impairment for both substances
Lormetazepam	Iudice et al. (2002)	Daytime vigilance Driving simulation	1 mg	No effect the next morning
Lormetazepam	Fabbrini et al. (2005)	SRT CRT		No effect
Temazepam Alcohol	Tiplady et al. (2003)		Temazepam: 20 or 30 mg BAC: 0.8–1.0 g/l	Temazepam slowed performance; alcohol generated more errors
Temazepam	Morin et al. (2003)		7.5 or 30 mg	Few effects and tolerance
Flunitrazepam Clonazepam	Dowd et al. (2002)	Behaviour and cognitive	Flunitrazepam: 2 mg Clonazepam: 3 mg	Flunitrazepam had an effect up to 4 hours after intake; clonazepam for 6 hours
Flunitrazepam	Bramness et al. (2006)	Blood level–impairment degree correlation		Clear correlation
Diazepam	Rich et al. (2006)	Memory	0.19 mg/kg	Impairment
Zolpidem Zopiclone Flunitrazepam	Bocca et al. (1999)		Zolpidem: 10 mg Zopiclone: 7.5 mg Flunitrazepam: 1 mg	Residual effects in morning for zopiclone and flunitrazepam
Lorazepam Flurazepam Nitrazepam Temazepam	Vignola et al. (2000)	Memory Attention Psychomotor function		Unmedicated insomniacs performed worse than medicated ones
Temazepam Triazolam Alcohol	Simpson and Rush (2002)		Temazepam: 15 or 30 mg Triazolam: 0.125 or 0.25 mg BAC: 0.5 g/l	Temazepam and triazolam alone had some impairment, but a worse impairment when combined with alcohol
Zolpidem Temazepam	Partinen et al. (2003)		Zolpidem: 10 mg Temazepam: 20 mg	No difference between drugs and placebo

TABLE A8 (continued)

Substance	Study	Tests	Doses	Effect
Zolpidem Zopiclone Lormetazepam	Allain et al. (2003)	LMT CTT SRT Sternberg test	Zolpidem: 5 mg Zopiclone: 3.75 mg Lormetazepam: 1 mg	Lormetazepam impaired performance on LMT
11 benzodiazepines	Vermeeren (2004)		Zaleplon: 10 or 20 mg Temazepam: 20 mg Lorazepam: 1 mg Triazolam: 0.125 mg Etc.	Four benzodiazepines (triazolam 0.125 mg, midazolam 7.5 mg, temazepam 20 mg and lormetazepam 1 mg) were unlikely to have residual effects
Temazepam Diphenhydramine Valerian	Glass et al. (2003)	DSST Manual tracking	Temazepam: 15 or 30 mg Diphenhydramine: 50 or 75 mg Valerian: 400 or 800 mg	No impairment with valerian and diphenhydramine 50 mg
Zolpidem Zopiclone Lormetazepam	Staner et al. (2005)	Driving simulation EEG	Zolpidem: 10 mg Zopiclone: 7.5 mg Lormetazepam: 1 mg	Zolpidem had no effect
Zopiclone Zolpidem Flunitrazepam	Berthelon et al. (2003)	Collision anticipation	Zopiclone: 7.5 mg Zolpidem: 10 mg Flunitrazepam: 1 mg	Flunitrazepam had a negative effect
Melatonin Zaleplon Zopiclone Temazepam	Paul et al. (2003)	Serial reaction time Logical reasoning	Melatonin: 6 mg Zaleplon: 10 mg Zopiclone: 7.5 mg Temazepam: 15 mg	Melatonin showed no impairment
Zopiclone Zolpidem Flunitrazepam	Meskali et al. (2009)	Driving simulator	Zopiclone: 7.5 mg Zolpidem: 10 mg Flunitrazepam: 1 mg	No increase in the number of collisions. Higher speed with zopiclone and flunitrazepam
Zolpidem	Verster et al. (2007)			Zolpidem was safer than zopiclone and benzodiazepine hypnotics if taken before 8 hours of sleep
Gaboxadol Zopiclone Zolpidem	Leufkens et al. (2009)	Residual effects SDLP	Gaboxadol: 15 mg Zopiclone: 10 mg Zolpidem: 7.5 mg	Driving was impaired with gaboxadol. Significant impairment with zolpidem and zopiclone
Benzodiazepine hypnotics	Vermeeren and Coenen (2011)	Review		Effects may diminish as a result of tolerance, but tolerance may not be complete
Zopiclone Zolpidem Flunitrazepam	Berthelon et al. (2008)	Residual effects	Zopiclone: 7.5 mg Zolpidem: 10 mg Flunitrazepam: 1 mg	No residual effect on speed perception and collision estimation
Intermediate- and long-acting benzodiazepines	Maxwell et al. (2010)	Analysis of crash data		In combination with alcohol: greater odds of unsafe driver action
Dose-dependent driving impairment benzodiazepines	Bramness et al. (2002)	Apprehended drivers		Clear drug concentration effect
Benzodiazepines	Smink et al. (2008a)	Relation between blood concentration and sobriety tests		Observations significantly related to concentration
Benzodiazepine receptor agonists	Verster and Roth (2013)	Review SDLP		Blood concentrations correlate poorly with impairment

Abbreviations: BAC, blood alcohol concentration; CFF, critical flicker fusion; CRT, choice reaction time; CTT, critical tracking test; DSST, digit symbol substitution test; EEG, electroencephalography; LMT, learning memory task; SDLP, standard deviation of lateral position; SRT, simple reaction time.

TABLE A9

Results of experimental studies on antihistamines

Substance	Author	Tests	Doses	Effect
Diphenhydramine	Richardson et al. (2002)		50 mg twice daily	Impairment
Diphenhydramine	Turner et al. (2006)	Memory CRT DSST	50, 75, 100 mg	Impairment
Clemastine	Meltzer et al. (2003)		0.68 mg	Somnolence
Mequitazine	Didier et al. (2000)		5 mg twice daily	Less somnolence than first generation, not more than second generation
Mequitazine	Theunissen et al. (2006a)	SDLP	5, 10, 15 mg	Dose-related increase
Chlorpheniramine	Mochizuki et al. (2002)	PET		
Chlorpheniramine	Serra-Grabulosa et al. (2001)	Auditory attention	4 mg	Impairment
Chlorpheniramine	Tashiro et al. (2008)	Lane deviations	6 mg repetab	Increased lane deviations
Cinnarizine	Nicholson et al. (2002)	DSST	15, 30, 45 mg	No
Cinnarizine	Philipova et al. (2004)	DSST	20 mg	No
Cinnarizine	Schneider et al. (2003)	DSST	20 mg	No
Desloratadine	Nicholson et al. (2003)	CRT DSST	5 mg	No
Desloratadine	Berger et al. (2002)		5 mg	No
Desloratadine	Monroe et al. (2003)			No
Desloratadine	Satish and Streufert (2003); Satish et al. (2004)			No
Desloratadine	Valk et al. (2004)			No
Desloratadine	Bousquet et al. (2004)			No
Desloratadine	Berger (2005)		5 mg	No
Desloratadine	Limon and Kockler (2003)			No
Loratadine	Saint-Martin et al. (2004)		10 mg	Less somnolence
Ebastine	Herberg (2000)		10, 20, 30 mg	No
Ebastine	Hindmarch and Shamsi (2001)	CFF CRT Simulated car tracking task		No
Levocetirizine	Hair and Scott (2006)		5 mg	Somnolence
Cetirizine	Shamsi et al. (2001)	CFF CRT Tracking task	2.5, 5, 10 mg	No
Cetirizine	Martínez-Cócera et al. (2005)		10 mg	Somnolence
Cetirizine	Nordness and Zacharisen (2003)		50 mg	No
Cetirizine	Vermeeren et al. (2002b)	Standardised driving test	10 mg	Less impairment
Fexofenadine	Hindmarch et al. (2002)	CFF CRT Tracking task	360 mg	No
Fexofenadine	Ridout and Hindmarch (2003)		60–120 mg	No
Fexofenadine	Theunissen et al. (2006b)		360 mg	No
Fexofenadine	Ridout et al. (2003a)		180 mg	No
Fexofenadine	Mohler et al. (2002)	DSST		No
Mizolastine	Bachert et al. (2001)		10 mg	Low
Azelastine	Golden et al. (2000)			No
Review second generation	Lange and Bachert (2004)			Desloratadine, ebastine and fexofenadine had no effect
Fexofenadine versus cetirizine	Tashiro et al. (2004)	CRT SRT	Fexofenadine: 120 mg Cetirizine: 20 mg	Fexofenadine less impairing than cetirizine
Bepotastine versus cetirizine, fexofenadine and olopatadine	Takahashi et al. (2004)	Sedation Psychomotor performance	Bepotastine: 10 mg twice daily Cetirizine: 10 mg Fexofenadine: 60 mg twice daily Olopatadine: 5 mg twice daily	Olapatadine most impairing and bepotastine least impairing

TABLE A9 (continued)

Substance	Author	Tests	Doses	Effect
Levocetirizine versus desloratadine	Passalacqua and Canonica (2005)	Memory, attention, alertness		No
Cetirizine versus loratadine	Salmun et al. (2000)		Cetirizine: 10 mg Loratidine: 10 mg	Loratidine resulted in less somnolence
Inter-drug differences	Shamsi and Hindmarch (2000)			Fexofenadine and ebastine had the least effect
Prescription-event monitoring	Mann et al. (2000)			Fexofenadine and loratadine had the least effect
Letter	Ramaekers and Vermeeren (2000)			Fexofenadine, ebastine and loratadine had no effect
Desloratadine and levocetirizine	Layton et al. (2006)			Less sedation with desloratadine
Review	Meltzer (2005)			Fexofenadine, loratadine and desloratadine had no effect
Fexofenadine versus hydroxyzine	Tashiro et al. (2005)	BRT	Fexofenadine: 120 mg Hydroxyzine: 30 mg	Fexofenadine had no effect
Fexofenadine	Mansfield et al. (2003)		180 mg	No
Fexofenadine	Bower et al. (2003)			No
Fexofenadine versus olopatadine and chlorpheniramine	Kamei et al. (2003)	Sedation	Fexofenadine: 120 mg Olopatadine: 10 mg	Fexofenadine had no effect
Ebastine versus chlorpheniramine	Tagawa et al. (2002)	Cognitive impairment	Ebastine: 10 mg	Ebastine had no effect
Loratadine versus diphenhydramine	Kay (2000) Kay and Quig (2001)	Divided attention	Loratidine: 10 mg Diphenhydramine: 50 mg	Loratidine had no effect
Desloratadine versus diphenhydramine	Wilken et al. (2003)		Desloratidine: 5 mg Diphenhydramine: 50 mg	Desloratidine had no effect
Tolerance to cetirizine, mequitazine and dexchlorpheniramine	Theunissen et al. (2006a)	Driving impairment	Mequitazine: 10 mg Cetirizine: 10 mg Dexchlorpheniramine: 6 mg	Tolerance after 8 days
Levocetirizine versus diphenhydramine	Verster et al. (2003a)	Memory, attention, tracking, SDLP	Levocetirizine: 5 mg Diphenhydramine: 50 mg	Levocetirizine had no effect
Desloratadine versus diphenhydramine	Vuurman et al. (2004)	SDLP	Desloratidine: 5 mg Diphenhydramine: 50 mg	Desloratidine had no effect
Diphenhydramine versus second-generation antihistamines: a review	Bender et al. (2003)			No clear effect of diphenhydramine
Fexofenadine versus diphenhydramine and alcohol	Weiler et al. (2000)		Fexofenadine: 60 mg Diphenhydramine: 50 mg	Diphenhydramine had greater effect than alcohol
Review	Verster and Volkerts (2004b)			Fexofenadine and levoceterizine had no effect
Levocetirizine versus cetirizine, loratadine, promethazine	Hindmarch et al. (2001b)	CFF, CRT, continuous tracking task	Levoceterizine: 5 mg Cetirizine: 10 mg Loratidine: 10 mg Promethazine: 30 mg	Levoceterizine had no effect
Review	Moskowitz and Wilkinson (2004)			Effect depends on substance, generation and individual
Rupatadine Hydroxyzine	Vuurman et al. (2007)	SDLP	Rupatadine: 10 mg Hydroxyzine: 50 mg	No effect from rupatadine
Bilastine Hydroxyzine	Conen et al. (2011)	SDLP	Bilastine: 20 and 40 mg Hydroxyzine: 50 mg	No effect from bilastine

Abbreviations: BRT, brake reaction time; CFF, critical flicker fusion; CRT, choice reaction time; DSST, digit symbol substitution test; PET, positron emission tomography; SDLP, standard deviation of lateral position; SRT, simple reaction time.

TABLE A10

Results of experimental studies on performance effects associated with the use of antidepressants

Substance	Study	Tests	Doses	Effect
TCAs (general)	Podewils and Lyketsos (2002)	MMSE		None
Amitriptyline	Veldhuizen et al. (2006b)	SDLP	25 mg	Significant increase
Amitriptyline	Iwamoto et al. (2008a)	Road tracking performance	25 mg	Correlation between plasma concentration and road tracking performance
SSRIs (general)	Dumont et al. (2005)	Different tests CFF	Low dose High dose	Stimulation Impairment
Fluoxetine	Strik et al. (2006)	Stroop Visual verbal test Letter digit substitution	20–60 mg	None
Escitalopram	Rose et al. (2006)		10 mg	None
SSRI (general)	Wadsworth et al. (2005)			Impairment
Sertraline **Paroxetine**	Schmitt et al. (2002)	Vigilance Stroop	50–100 mg 40–60 mg	None
Sertraline	Constant et al. (2005)	Psychomotor slowing/ executive function	50–75 mg	Positive effect
Sertraline	Devanand et al. (2003)	Psychomotor slowing and executive function	50–200 mg	None
Citalopram	Harmer et al. (2002)	Memory	10 mg i.v.	Positive effect
Fluoxetine versus paroxetine	Cassano et al. (2002)	Cognitive function	Fluoxetine: 10–40 mg Paroxetine: 20–60 mg	None
Paroxetine	Hindmarch et al. (2000a)	Withdrawal		Impairment
SSRIs	Ravera et al. (2012)	Literature review		Inconsistencies between studies
Venlafaxine	O'Hanlon et al. (1998)	CFF, CTT, divided attention, Macworth	37.5–75 mg	None
Venlafaxine	Campagne (2005)	Withdrawal		Impairment
Milnacipran	Hindmarch et al. (2000b)	CFF	50 + 25 mg	None (young age) Positive effect (old age)
Milnacipran	Poirier et al. (2004)	CFF	50 mg twice daily	None
Milnacipran	Richet et al. (2004)		50 mg twice daily	No effect and no potentiation
Fluoxetine versus reboxetine	Gallassi et al. (2006)		Fluoxetine: 10–40 mg Reboxetine: 4–8 mg	Improvement
SSRI versus SNRI	Wingen et al. (2006a)			Impairment
Reboxetine **Mirtazapine**	Brunnauer et al. (2008)	Driving skills Frequency of accidents		Patients improved in driving skills. Frequency of accidents decreased
Newer antidepressants	Brunnauer and Laux (2013)	Systematic review		SSRIs and venlafaxine had no deleterious effects. Acute use of mirtazapine led to impairment
All antidepressants	Ramaekers (2003b)	SDLP		Sedating antidepressant led to impairment Non-sedating antidepressant had no effect SSRI (mirtazapine) was less impairing than TCA (SNRI)
All antidepressants	Brunnauer et al. (2006)	Fitness to drive		Less impairment for patients treated with SSRIs or mirtazapine when compared with TCAs or venlafaxine
Paroxetine versus mirtazapine	Ridout et al. (2003b)	BRT, CFF, CRT	Paroxetine: 20 mg Mirtazapine: 15–30 mg	No effect for paroxetine
Fluvoxamine versus imipramine	Koetsier et al. (2002)	CPT		Improvement for both

TABLE A10 (continued)

Substance	Study	Tests	Doses	Effect
Fluoxetine versus desipramine	Levkovitz et al. (2002)	Memory	Fluoxetine: 20 mg Desipramine: 125–200 mg	Improvement with fluoxetine was greater than with desipramine
Fluvoxamine versus dothiepine	Wilson et al. (2000)	Sleep	Fluvoxamine: 100 mg Dothiepine: 100 mg	Fluvoxamine decreased; dothiepine increased
Reboxetine versus imipramine	Katona et al. (1999)	Somnolence	Reboxetine: 4–6 mg Imipramine: 50–100 mg	Reboxetine had no effect
TCA and SSRI	Peretti et al. (2000)	CFF threshold BRT		TCA decreased CFF; BRT impaired
Paroxetine versus nortriptyline	Nebes et al. (2003)	Cognitive function in elderly		No change
Sertraline, fluoxetine and nortriptyline	Doraiswamy et al. (2003)	Cognitive function	Sertraline: 50 mg Fluoxetine: 20 mg Nortriptyline: 25 mg	Improvement
Venlafaxine and dothiepine	Trick et al. (2004)	Cognitive function: CFF	Venlafaxine: 37.5 mg twice daily Dothiepine: 25 + 75 mg	No disruptive effect
Paroxetine and nortriptyline	Butters et al. (2000)	Memory and executive function		Improvement
Escitalopram versus mirtazapine	Wingen et al. (2006b)	Delayed verbal memory score	Escitalopram: 10–20 mg Mirtazapine: 30–45 mg	Escitalopram had no influence
Sertraline versus nortriptyline	Coffey et al. (2002)	Shopping list task, DSST, MMSE	Sertraline: 50–100 mg Nortriptyline: 25–100 mg	Sertraline had a more positive effect
Paroxetine, amitriptyline	Iwamoto et al. (2008b)	Road-tracking and car following	Paroxetine: 10 mg Amitriptyline: 25 mg	Paroxetine caused no impairment
Tianeptine versus mianserin	Ridout and Hindmarch (2001)	CRT, CFF, BRT	Tianeptine: 12.5–37.5 mg Mianserin: 30 mg	Tianeptine had no effect
Hypericum perforatum	Timoshanko et al. (2001) Siepmann et al. (2002)	DSST	900–1800 mg Extract: 255–285 mg	Impairment None
Moclobemide	Siepmann et al. (2004)	CFF, CRT, memory	150 mg twice daily	None
Mirtazapine	Shen et al. (2009)		30 mg	Increase in driving safety among depressed patients
Esmirtazapine	Ramaekers et al. (2011)	SDLP Residual effects	1.5 and 4.5 mg	1.5 mg: no increase in SDLP 4.5 mg: increased SDLP, but this resolved after repeated doses

Abbreviations: BRT, brake reaction time; CFF, critical flicker fusion; CPT, continuous performance test; CRT, choice reaction time; CTT, critical tracking test; DSST, digit symbol substitution test; i.v., intravenous; MMSE, mini-mental state examination; SDLP, standard deviation of lateral position; SNRI, serotonin/noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

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European Monitoring Centre for Drugs and Drug Addiction
Drug use, impaired driving and traffic accidents
Luxembourg: Publications Office of the European Union
2014 — 149 pp. — 21 × 29.7 cm

ISBN 978-92-9168-687-2
doi:10.2810/26821

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TD-XD-14-016-EN-N

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