



European Monitoring Centre  
for Drugs and Drug Addiction

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EMCDDA

# INSIGHTS

Drug use, impaired driving  
and traffic accidents

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Drug use, impaired driving and traffic accidents

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## Foreword

The mobility provided by road transport, particularly the passenger car, allows many modern Europeans to enjoy a lifestyle characterised by flexibility and independence. However, if we count up the lives lost and injuries inflicted in road traffic accidents, it is clear that this comes at a price, with the most recent statistics revealing that more than 40 000 people die on European roads each year, while a further 1.7 million are injured. No less than a quarter of these deaths, some 10 000 per year, are estimated to be caused by drink-driving. And although alcohol is by far the most prevalent and well-documented psychoactive substance affecting drivers, concerns have been mounting about increasing reports of road deaths linked to illicit or medicinal drugs. Public awareness of the role of psychoactive substances other than alcohol in road traffic accidents has increased, due to attention given to this issue by the media, and policymakers are increasingly called upon to respond to this problem.

In the European road safety programme tabled in 2003, the European Union set itself the ambitious target of halving the number of road deaths by the end of the decade, thereby saving up to 20 000 lives in 2010. In recognition of the growing problem of driving under the influence of psychoactive substances, including illicit drugs and medicines, and the urgent need to establish a firm understanding of this issue, the programme proposed a range of measures designed to improve and share information on driving under the influence of drugs as a cause of road accidents. Also in 2003, the European Council called on the Commission to ensure that the current programme on road safety is followed up by a set of actions to combat the impact of psychoactive substance use on road accidents. An essential step in this direction is currently being taken under the DRUID project, reporting in 2010, which aims to fill gaps in the knowledge base, thereby enabling the development of harmonised, EU-wide regulations for driving under the influence of alcohol, drugs and medicine. Driving under the influence of drink, drugs and medicines is also targeted in the EU drugs strategy 2005–12 and the EU drugs action plan 2005–08.

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 EMCDDA has undertaken to update its 1999 literature review on drugs and driving. This edition of the Insights series is the result of that update. Together with the EMCDDA's 2007 Selected issue on the use of cannabis and benzodiazepines by drivers, the present report provides a comprehensive picture of the European situation on illicit drugs and medicines

in connection with driving. Both the policymaker and the general reader will find summarised here the large number of studies that have been published on the topic since 1999, 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.

Though 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.

I wish to thank the following people: Elke Raes, T. Van den Neste and A.G. Verstraete, who conducted the literature survey and prepared the text; Dominique Lopez and Brendan Hughes, who managed the project under the direction of Paul Griffiths; Shazia Qureshi for editing the text; and Fiona Brown and Peter Fay, who coordinated its publication.

**Wolfgang Götz**

Director of the EMCDDA



## Introduction

In the EU Member States, concern about the role of drugs in driver impairment and traffic accidents has continuously increased. In 1999, a study of drug use among drivers in different European countries concluded that, in the general driver population, the prevalence of illicit drug use was probably in the range 1–5%, whereas licit drug use was in the range 5–15% (Verstraete, 2003).

The first report by the 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 2000–04 reflected this need, calling for research into the effects of driving under the influence of illicit drugs and certain psychoactive medicines <sup>(1)</sup>. Meanwhile, countries have tightened laws, increased penalties or altered national road safety or drug strategies to address the problem (EMCDDA, 2007). However, individual countries' legal responses to drug-impaired driving vary greatly, from zero-tolerance laws (sanctioning detection of the substance per se) to impairment laws (sanctioning if the person is deemed unfit to drive). Possible penalties are also markedly different between countries <sup>(2)</sup>.

By 2007, a wealth of European and world research had addressed the issue and an update of the EMCDDA (1999) report was justified. The main objectives of the present report are to review the current knowledge on driver impairment due to drug use from experimental and epidemiological studies published since 1999, 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.

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<sup>(1)</sup> Action 3.1.2.5.

<sup>(2)</sup> See ELDD Topic overviews (<http://emcdda.europa.eu/publications/legal-reports>).

The coverage of the initial European literature review has been widened to include studies from Australia, Canada and the United States. The scope of substances discussed has also been widened because of concern about the increasing use of stimulants in Europe, as well as the problem use of benzodiazepines. Cocaine, opiates and substances used in substitution treatment (methadone, buprenorphine) have been added, and the distinction between long-, medium- and short-acting benzodiazepines is now acknowledged. Thus, this report encompasses the main psychoactive substances found in Europe.

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 1999) according to the type of drivers surveyed and provides an overview of the differences found depending on the sample, screening, design of the study, etc. Finally, 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. The report concludes by outlining the various responses available to national authorities.

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 EU's roadside testing assessment projects considered no device reliable enough for roadside screening. For an overview of the different issues at stake, the reader can refer to the Rosita project <sup>(3)</sup>. For the legal aspects, which are also not addressed in this publication, the ELDD provides a comprehensive overview of the wide variety of legal mechanisms used to sanction drugs and driving in the EU and Norway.

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).

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<sup>(3)</sup> <http://www.rosita.org/>

## How studies were selected for this report

This report is the result of an inventory of the existing literature published in Europe, the United States, Canada and Australia, mainly in the English language.

A database was created consisting of relevant articles from ISI Web of Science, PubMed (Medline), Psychinfo and Transport, relevant reports, relevant conference proceedings of ICADTS, TIAFT etc., relevant books, reference lists of relevant reviews and other sources of information. The following terms or combinations of these terms were used in the search strategy: 'drug\*', 'narcotic\*', 'medicin\*', 'alcohol', 'marihuana', 'marijuana', 'cannabis', 'cannabinoids', 'THC', 'opiates', 'morphine', 'methadone', 'heroin', 'benzo\*', 'amphetamine\*', 'MDMA', 'MDA', 'MDEA', 'MBDB', 'cocaine', 'benzoyllecgonine', 'antidepressants', 'antihistamines', 'GHB', 'ketamine', 'fentanyl', 'ephedrine', 'phentermine', 'epidemiological', 'experimental', 'driving\*', 'driver\*', 'accident', 'psychomotor\*', 'cognitive', 'impairment', 'test battery', 'roadside', 'influence', 'alcolock', 'alcohol ignition interlock', 'BAC'.

Only the references published since the writing of *Literature review on the relation between drug use, impaired driving and traffic accidents* (EMCDDA, 1999) and those relevant for the update of the report, were taken into consideration.

For meta-analyses, odds ratios and relative risks were calculated using the statistical programme MedCalc.



## Executive summary

This literature review provides a comprehensive report on the relationship between drug use, impaired driving and traffic accidents. It covers methodological issues (Chapter 1), presents results of prevalence surveys among drivers and provides an overview of findings from major international epidemiological surveys published since 1999 (Chapter 2), and also gathers evidence from experimental and field studies of the relationship between drug use, driving impairment and traffic accidents (Chapter 3).

The research here can be broadly separated into experimental and epidemiological studies. Every approach has its inherent advantages and disadvantages. Experimental studies may be set in a laboratory, in a driving simulator, or on the public road, and the drug is administered in measured doses to volunteers. They can result in an interpretation by single cause, but can only identify potential risks, and the results can in some cases be of limited value because of the use of non-realistic doses, or because of the drug use history or inter-individual differences of the volunteers. Epidemiological studies examine the prevalence of drugs 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, they may contain risk factors that cannot be eliminated by study design, and that may be indistinguishable from factors that are highly correlated with the risk factor. Between studies, results may be incomparable due to testing different populations, different kinds of samples, etc.

The results of experimental studies indicated that several illicit drugs can have an influence on driving performance; some drugs, but not all, show effects that are dose-dependent. Cannabis can impair some cognitive and psychomotor skills that are necessary to drive. MDMA exhibits both negative and positive effects on performance, while studies investigating the effects of a combination of alcohol and illicit drugs found that, in such cases, some illicit drugs (for example, cannabis) can cause additional, synergistic impairment, while others (for example, cocaine) can partially reverse the 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 obvious impairment for some therapeutic drugs. Benzodiazepines generally have impairing effects, but some types (whether long-, medium- or short-acting) cause severe impairment while 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 show more impairment than the more recent types, though the results of experimental tests after consuming SSRIs 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. About 1 % to 2 % of drivers stopped during roadside surveys test positive for drugs in saliva, though one outlier returned a figure of 11 %. Driving under the influence of a combination of alcohol and drugs is not uncommon. Studies assessing the prevalence of drugs, medicines and/or alcohol in drivers who were involved in a traffic accident (fatal or otherwise) found that alcohol is more prevalent than any other psychoactive substance, but drugs are also frequently found, and in a higher number of samples than in the general driving population. Of the drugs analysed, cannabis is the most prevalent after alcohol, though when samples were analysed for the presence of benzodiazepines, they were sometimes even more prevalent than cannabis. Statistically, increased accident risks and/or risks of being responsible for an accident were found for cannabis, benzodiazepines, amphetamines, heroin and cocaine, and many of these risks increase when the drug is combined with another psychoactive substance, such as alcohol.

The results of both epidemiological and experimental studies should be combined to obtain a good estimate of the impact of certain drugs on driving performance and accident risk. To obtain more compatible methodologies, in 2006–07 a committee of international experts, including representatives from the EMCDDA and NIDA, drafted guidelines for future research into drugs and driving. These have been taken on board by the DRUID project, a large-scale EU funded project that will conduct reference studies of the impact on fitness to drive for alcohol, illicit drugs and medicines, but also analyse the prevalence of alcohol and other psychoactive substances in drivers involved in accidents and in the general driving population, and calculate analytical and risk thresholds for several illicit drugs and medicines in several European countries. DRUID will be completed in 2010.



# Chapter 1: Methodological issues in determining the relationship between drug consumption, impaired driving and traffic accidents

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# Chapter 1: Methodological issues in determining the relationship between drug consumption, impaired driving and traffic accidents

In order to study driving under the influence of drugs (DUID), several methods are used. These can largely be 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 is administered in different doses to volunteers and the effects on performance are measured and compared to placebo or a positive control (for example, 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.

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

- Often the drug doses administered have a lower potency than those used in the street. For example, performance studies for cannabis traditionally used low-potency cannabis with a maximum 4%  $\Delta^9$ -tetrahydrocannabinol (THC). Ramaekers et al. (2006a) showed that high-potency cannabis (13% THC) diminishes additional cognitive functions and has a more pronounced effect on performance, compared to results from previous studies that used low-potency cannabis. 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 <sup>(4)</sup> 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 this function (Lamers et al., 2003). Other possible causes of discrepancies in results in these studies could include differences in drug type, dose and task.
- Results of experimental studies assessing acute effects of drugs in recreational drug users may be influenced by the subjects' drug use history. For example, Rush et al. (1999) found no effect of oral cocaine on performance on the DSST, while two previous studies found an improvement. The subjects in both previous studies reported substantially less cocaine use than the subjects used by Rush et al. (1999), and the authors suggested that perhaps their subjects were 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 to their pretest baseline performance (Swerdlow et al., 2003). Mattay et al. (2000) showed that in normal subjects, the behavioural and neurophysiological effects of dextroamphetamine are not homogeneous because of genetic variation and differences in baseline cognitive capacity.
- Experimental studies can only identify 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.

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<sup>(4)</sup> Dextroamphetamine is the d form of amphetamine (the new terminology refers to the S form). <http://www.emcdda.europa.eu/publications/drug-profiles/heroin>

The advantage of experimental research is that it offers the chance to work on far more differentiated questions and less frequently occurring risk factors compared to epidemiological research. Another advantage is that experiments, with an adequate design, can result in an interpretation by a single cause, 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

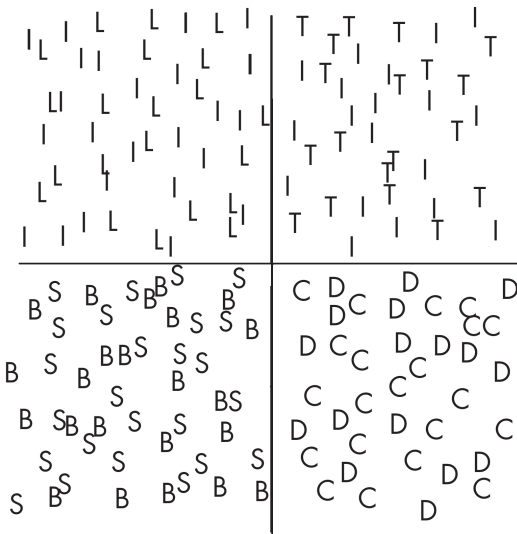
Cognition is the conscious process of knowing or being aware of thoughts or perceptions, including understanding and reasoning. Cognitive tests can assess a variety of cognitive functions:

- **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



**Figure 1:** Four examples of a letter cancellation task.

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).
- 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, and target sequences of numbers must be detected with the press of 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 ability to recall the previously acquired responses.
- Sternberg test: this test explores short-term memory and working memory. A series of 2–6 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 preplan 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.

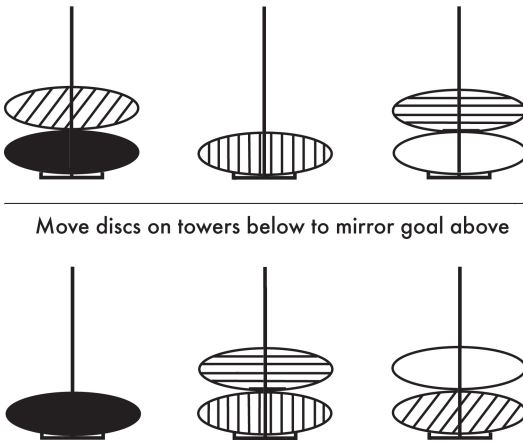


Figure 2: A Tower of London test.

### Psychomotor tests

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

- Body sway: measurements of body movement of the subject with or without 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. As each light is illuminated in random order, the subject must trigger a switch corresponding to that light.
  - ◇ The grooved pegboard test is a manual dexterity test consisting of 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 numbers and 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 screen, 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 mental receiving of a sensory impression (visual, auditory or somatosensory) and the execution of a movement in response to that impression.
  - ◇ 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 pre-selected 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 MRT from 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 while decks C and D are 'advantageous'. One dependent measure is collected from this task: net score (total number of cards picked from C and D minus 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





**Figure 3:** A visual analogue scale for the subjective feeling of 'high'.

normal state of mind before treatment was started (Figure 3). Another example is the Stanford sleepiness scale, a 7-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 only measure 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, sometimes an additive or even synergistic effect is found, while other studies find the opposite. Liguori et al. (2002) 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 with 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 gained 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 last 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 five 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 drop-out rate. They found that without the simulator training programme, the drop-out rate due to 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. (2006b) evaluated the effect of chronic nonmalignant 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., 2006b):

- 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, basic vehicle control, such as road tracking, is required, involving automatic or effortless performance. Further, negotiation of common driving situations, such as curves, intersections and gap acceptance, requires controlled processing and thus more effort. Also, subjects are required to determine motivational aspects (i.e., to specify the risk they are willing to take) and risk evaluation. Since 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 for revealing THC's adverse effects 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 if 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 in the general driving population to the prevalence in persons admitted to an emergency department, an estimation can be made of the risk of being injured by 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, gender, etc. One study reporting results of drivers who were killed in traffic accidents in France only included 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 differ in which samples are collected, 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, opiates 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 DUI reported only the percentage of samples that were positive for diazepam and flunitrazepam, while in a study in Switzerland, the samples were analysed for diazepam, desmethyldiazepam, midazolam, oxazepam and lorazepam (Augsburger et al., 2005; Christophersen, 2000). For cannabis detection, some studies only test for the presence of THC, while others test for the THC metabolites THC-COOH (11-nor- $\Delta^9$ -THC-9-carboxylic acid) or 11-OH-THC (11-hydroxy- $\Delta^9$ -THC) 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 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 than when blood or saliva are sampled (Verstraete, 2004).

- 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 ‰ (Logan and Schwilke, 2004; Logan, 2005; Plaut and Staub, 2000) to 0.8 ‰ (Assum et al., 2005; Brault et al., 2004; del Rio et al., 2002; Longo et al., 2000a).

All of these factors can influence the outcomes of epidemiological studies, making it nearly impossible to compare results. Thus, there is a need for methodological guidelines (see section below on recent proposal pertaining to research).

In what follows, the methodology and limitations of the various types of epidemiological studies are described, as are recent proposals regarding research and methodological guidelines.

### Roadside surveys

Roadside surveys investigate the prevalence of psychoactive substances in 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. A 2003 study found that random roadside testing was allowed in nine countries in Europe: Belgium; Denmark; Finland; Germany; Italy; Luxembourg; Norway; Portugal and Spain. In the Netherlands, roadside surveys may only be used for scientific research, and in five other countries, some suspicion is needed: Ireland; France; Austria; Sweden and the United Kingdom (EMCDDA, 2003) <sup>(5)</sup>.

<sup>(5)</sup> <http://www.emcdda.europa.eu/publications/topic-overviews/driving>

## 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 may have been administered in hospital or at the crash site 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 necessity to distinguish whether positive test results for medicines were because of initial use by the driver or a result of therapeutic administration during emergency care or reanimation 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 DUI: 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.

A possible difficulty of studies that try to assess the prevalence of psychoactive substances in drivers who were injured or killed by a traffic accident is the necessity of distinguishing whether positive test results for medicines were from pre-injury use, or therapeutically administered 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 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

The accident risk associated with the use of drugs, medicines and/or alcohol can be assessed by comparing their prevalence in the general driving population (controls) to the prevalence in 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). OR and RR 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, using, for example, 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).

**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	$a+c$	$b+d$	$n$

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 dropouts. As most of the substances under investigation are illicit, it is probable that potential controls who are users would be 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. Since generally, the proportion of non-crash drivers who test positive for drugs is likely to be small, even a relatively small proportion of potential controls who do not supply a sample would throw study results into serious doubt (Bates and Blakely, 1999).

Ramaekers (2003b) 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, use of tricyclic antidepressants (TCA) 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 limited.

## Responsibility analysis

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 in drivers who were responsible for a traffic accident (cases) is compared to the prevalence in drivers who were involved in, but not responsible for a traffic accident (controls).

There are a number of limitations to responsibility analyses:

- Some cases can be misjudged on the real responsibility, 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 that were judged 'not responsible' may, in fact, have borne some responsibility, since 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 to 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 being responsible 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 odds ratios and 95% confidence intervals 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 or 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 the 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).

## Recent proposals pertaining to research

Because of the many limitations that are inherent to epidemiological and experimental studies, it is difficult to compare or combine the results of the different studies. Recent proposals to improve research are described below.

### Driving skills in opioid-dependent patients

In their review of studies of impaired driving skills in opioid-dependent/tolerant patients, Fishbain et al. (2003) listed many confounders that might have influenced the results. They also made several recommendations for future research to address these confounders:

- Future psychomotor and cognitive studies should control for pain levels, educational status and history of drug/alcohol abuse/dependence, in addition to sex and age.
- The types of control groups used can be improved upon. When a treatment group of patients taking opioids is compared to a control group of patients not on opioids, the effects of a patient's disease state, e.g. cancer (fatigue, etc.), pain, etc., are not controlled for. A better control group might use patients as their own controls. As such, psychomotor and cognitive studies should be conducted both before and after opioid use. Another possible improvement to this type of research would be

to include a patient control group. For example, when comparing cancer patients using opioids to non-patient opioid-free controls, a control group of opioid-free cancer patients might be added to control for the patients' disease state. A third improvement would be the use of positive controls as a benchmark. Patients in the positive control group would be given drugs such as diazepam that are known to affect cognitive and psychomotor performance. Opioid effects then would not only be compared to opioid-free controls, but also to this positive control group.

## Research into drugs and driving

Berghaus et al. (2007) describe the principal methodological approaches of epidemiological research and the optimal design of an experimental study. Optimal methods for the collection of the data, analysis of results, ethical issues and quality control of different kinds of epidemiological research, namely roadside surveys, case-control studies, responsibility analysis and pharmacoepidemiological studies, and of experimental studies are described.

In the United States, Lacey et al. (2007) developed and tested procedures to enhance roadside surveys to include collecting oral fluid and blood samples from the night-time weekend driving population and testing them for drugs as well as alcohol. In the past, roadside surveys have been used to measure the extent of alcohol use in the night-time driving population in order to establish regular measures of that activity, which is a measure of progress in reducing impaired driving. The findings indicated that this form of expanded roadside survey is practicable in the United States and may be used in the next full-scale national roadside survey.

In June 2005, the International Council on Alcohol, Drugs, and Traffic Safety's (ICADTS) Working Group on Illegal Drugs and Driving recognised a critical need for standards or guidelines for research into drugs and driving and recommended that international researchers meet to develop them. The meeting, held in September 2006, resulted in a set of standards for future research into drugs and driving <sup>(6)</sup> that should improve the comparability of data globally. The standards consist of recommendations on three different topics: behaviour (around 30 recommendations), epidemiology (40 recommendations) and toxicology (more than 60 recommendations) (NIDA, 2007). The experts in attendance represented nine countries on three continents, and the meeting was co-sponsored by the National Institute on Drug

<sup>(6)</sup> A modified Delphi method was used to develop an initial set of draft standards.

Abuse (NIDA), the European Commission, EMCDDA, ICADTS, the International Association of Forensic Toxicologists (TIAFT) and the French Society of Analytical Toxicology (SFTA).

## 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 performance tests, tests in a driving simulator or 'real' driving tests. While these studies allow the assessment of the effects of a drug on differentiated functions, they can only identify potential risks, but with an adequate design, they can result in an interpretation by 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, visual-motor coordination skills, etc. 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 necessity of taking traffic safety into consideration.

Because of small sample sizes and a multitude of variable factors in experimental studies, it is difficult to compare or combine 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, samples are tested for different psychoactive substances.

Guidelines have recently been developed for future research into drugs and driving that aim to improve the comparability of studies.





## Chapter 2: Prevalence of drugs in drivers

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## Chapter 2: Prevalence of drugs in drivers

In order to estimate the size of the danger that driving under the influence of drugs poses for 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 1999 are discussed in this chapter. A more detailed description of the types, methodology and limitations of these types of studies is given in Chapter 1.

### Roadside surveys

Roadside surveys investigate the prevalence of psychoactive substances in 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 Table A1 (Appendix). Eight studies were found that were published since 1999. One study was conducted in Australia (P. Swann, personal communication), one in Canada (Dussault et al., 2002), one in Denmark (Behrendorff and Steentoft, 2003), two in the Netherlands (Assum et al., 2005; Mathijssen, 1999), one in Norway (Assum et al., 2005), one in the United Kingdom (Glasgow) (Assum et al., 2005) and one in the United States (Lacey et al., 2007).

It is difficult to compare the results of the different studies, because of the many differences in methodology (see Chapter 1). There are, however, some similarities. In most of these studies, the drug that is most frequently detected in the general driving population is cannabis. However, in Australia, methamphetamine was more prevalent, and in the United Kingdom, 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethylamphetamine (MDEA) and MDMA were more prevalent than cannabis. The study in Australia only tested for the presence of cannabis and methamphetamine. Moreover, oral fluid was tested using oral fluid screening devices, and only positive samples were sent to the laboratory for confirmation. The lower prevalence of cannabis than of methamphetamine in the Australian study could be due to the low sensitivity of the oral fluid screening devices for cannabis. In the United Kingdom study, no explanation was found for the higher prevalence of amphetamines compared to cannabis.

Benzodiazepines are the second most prevalent drug/medicine found in drivers in Canada, Denmark, the Netherlands (2000–04) (Assum et al., 2005) and Norway.



However, in Norway, opiates were as prevalent as benzodiazepines. In the 1997–98 study in the Netherlands (Mathijssen, 1999), cocaine was the second most prevalent drug after cannabis. However, the difference between the percentage of cocaine-positive and benzodiazepine-positive urine samples was small, as there were six urine samples positive for cocaine and five for benzodiazepines. In the study conducted in the United States, cannabis was the most prevalent drug, followed by cocaine and amphetamines, both present in the same number of samples. But given that it was a pilot study, the results should be interpreted with caution. In addition, the aim was to develop and test procedures that would be used in the next full-scale national roadside survey; the results are thus not representative of the American driving population as a whole.

The data in Table A1 (Appendix) also show that the combination of alcohol and drugs is prevalent in about 0.3% to 1.3% of the general driving population. The percentage of drug-positive drivers ranged from about 1% to 15%. About 1% to 2% of drivers stopped during roadside surveys tested positive for drugs in saliva. In Canada, the Netherlands and the United States, the percentages were relatively high, possibly because of these methodological reasons:

- the 1997–98 study in the Netherlands (Mathijssen, 1999) and the study in the United States were conducted on weekend nights;
- the study in Canada and both studies in the Netherlands used urine as the biological sample, which has a longer detection time.

## Subsets of drivers

### Drivers injured in traffic accidents

Table A2 (Appendix) shows nine studies on drug prevalence in injured drivers published since 1999: one in Australia (Longo et al., 2000a); one in Denmark (Bernhoff et al., 2005); two in France (Kintz et al., 2000; Mura et al., 2003); one in the Netherlands (Assum et al., 2005); one in South Africa (Sukhai, 2004) and three in the United States (Lowenstein and Koziol-McLain, 2001; Soderstrom et al., 2001; Walsh et al., 2005).

Drugs and/or alcohol were frequently detected in injured drivers, more frequently than in the general driving population. This is particularly shown by the results of the study conducted in 2003 in the United States by Walsh et al. (2005). About half of the injured drivers in this study tested positive for drugs, higher than the percentage

of alcohol-positive drivers (30.6%). Cannabis was the most frequently detected drug in most of the studies, with a maximal prevalence of 26.9% in the 2003 study in the United States (Walsh et al., 2005). In the 1994–96 study in the United States (Soderstrom et al., 2001), however, opiates were detected in 23.7% of blood samples, cocaine in 18.7% and cannabis in only 9.6%. However, in this latter study, only 58% of eligible, injured patients were approached and screened for drugs, raising questions about selection bias.

Benzodiazepines were the most frequently detected drug in the 2000–01 study in France (Mura et al., 2003) and in the Dutch study.

In all studies that tested for alcohol as well as drugs, alcohol was found in a higher percentage of samples than any other drug, except in one American study (Lowenstein and Koziol-McLain, 2001) in which cannabis was more prevalent than alcohol. The combination of alcohol and drugs was also frequently encountered, with prevalence ranging from 1.4% to almost 20%. There is large variation in the percentages of drug-positive samples in the different studies, but this is probably due to 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 that were killed in traffic accidents are given in Table A3 (Appendix). Eleven studies have been published since 1999: one in Australia (Drummer et al., 2003); one in Canada (Brault et al., 2004); one in France (Mura et al., 2006); one in Hong Kong (Cheng et al., 2005); two in Italy (Sironi et al., 1999; Vignali et al., 2001); two in Spain (del Rio et al., 2002; Lopez-Rivadulla and Cruz, 2000); one in Sweden (Holmgren et al., 2005); one in the United Kingdom (Assum et al., 2005) and one in the United States (Logan and Schwilke, 2004; Logan, 2005).

Alcohol was the most frequently detected psychoactive substance in drivers killed in accidents. However, drugs were also frequently detected, and just as in injured drivers, at a higher prevalence rate than in the general driving population. The combination of alcohol and drugs was also prevalent in a substantial number of samples, ranging from 2.5% to 17%. In five studies, cannabis was the most prevalent drug, with a maximal value of about 29% in the study in France. In this study, however, only drivers younger than 30 years were included, which may partially explain the high number of cannabis-positive samples.

### Drivers involved in traffic accidents

Table A4 (Appendix) shows the results from four studies of drivers involved in traffic accidents published since 1999: three in France (Laumon et al., 2005; Pépin et al., 1999, 2003) and one in Greece (Maravelias, 2003).

The data from these studies are in agreement with the findings from the studies of drivers injured or killed in traffic accidents. Alcohol is more prevalent than any other psychoactive substance, cannabis is the most prevalent after alcohol (however, the studies in France did not test for benzodiazepines, and benzodiazepines were as prevalent as cannabis in Greece) and the combination of alcohol and drugs is detected in a substantial number of samples.

### Drivers suspected of driving under the influence of drugs

Table A5 (Appendix) shows 15 studies published since 1999 of drivers stopped on suspicion of drug use: one in Australia (Kotsos et al., 2003); two in Belgium (Maes et al., 2003; Raes and Verstraete, 2005); one each in Finland (Lillsunde, 2000); France (Pépin et al., 1999); Germany (Toennes et al., 2005); Iceland (Thorsdottir et al., 2004); Luxembourg (Wennig, 2005); the Netherlands (Smink et al., 2001); Norway (Christophersen, 2000); and Slovenia (Zorec-Karlovsek et al., 2003), and two studies in both Sweden (Ceder, 2000; Jones, 2005) and Switzerland (Augsburger et al., 2005; Plaut and Staub, 2000).

The studies show a large variation in the number of drug-positive samples found on suspicion (55% to 99%). 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).

In all the studies where samples were tested for alcohol and drugs, a psychoactive substance other than alcohol was most frequently detected, except in one study in Switzerland (Plaut and Staub, 2000) in which alcohol was most prevalent. In this study, this was probably due to the very low cut-off level used to detect alcohol (BAC > 0.1 ‰).

Cannabis is the most frequently detected psychoactive substance in eight studies. In both studies in Sweden, amphetamines were the most frequently encountered drug; Jones (2005) remarks that this has been so for several decades. In the Netherlands, cocaine was the most prevalent drug, but benzodiazepines were almost as prevalent. Smink et al. (2001) remark that the situation in the Netherlands is different from that

in neighbouring countries, where cannabis is most frequently encountered. In France and Germany, cannabis was most frequently encountered, but samples were not tested for the presence of benzodiazepines. Cannabis was also the most prevalent drug in Norway, but samples were not tested for cocaine.

In the study in Australia, blood samples were only collected from drivers who had failed the field sobriety test. As drugs were found in 99% of the blood samples, Kotsos et al. (2003) concluded that the field sobriety test used in the study is an effective initial method for detecting drug use.

In Sweden, an increase in the prevalence of amphetamines and cannabis was detected after the implementation of new zero tolerance legislation for narcotic drugs, while there was no change in the prevalence of therapeutic drugs. According to Ceder (2000), this may be because police in Sweden were allowed to carry out eye examinations on drivers following the change in legislation, as amphetamines and cannabis have a pronounced effect on pupil size and reaction to light.

### **Drivers suspected of driving under the influence of alcohol**

Three epidemiological studies have been published since 1999 investigating the presence of drugs in biological samples of drivers suspected of driving under the influence of alcohol in Table A6 (Appendix). Two studies were conducted in Germany (Rentsch et al., 2002; Römhild et al., 2005) and one in the United Kingdom (Scotland) (Officer, 2003). The data show that drivers stopped on suspicion of alcohol use are frequently under the influence of drugs. Cannabis is the most frequently detected drug in these samples.

In Ireland, Fitzpatrick et al. (2006) analysed samples from drivers suspected of driving under the influence of an intoxicant. Of these, 1 000 drivers were below the legal limit for alcohol and 1 000 were over the limit. The samples were tested for the presence of amphetamines, methamphetamines, benzodiazepines, cannabinoids, cocaine, opiates and methadone. The results showed that the prevalence of drugs decreased steadily as alcohol concentrations increased. Of the drivers under the legal limit for alcohol, 33% tested positive for drugs; this figure was 14% among drivers over the limit. Being under the legal limit for alcohol, stopped in a city area, stopped between 6.00 a.m. and 4.00 p.m., stopped between 4.00 p.m. and 9.00 p.m., and younger age was each independently associated with a positive drug test.

## Surveys on driving under the influence of drugs

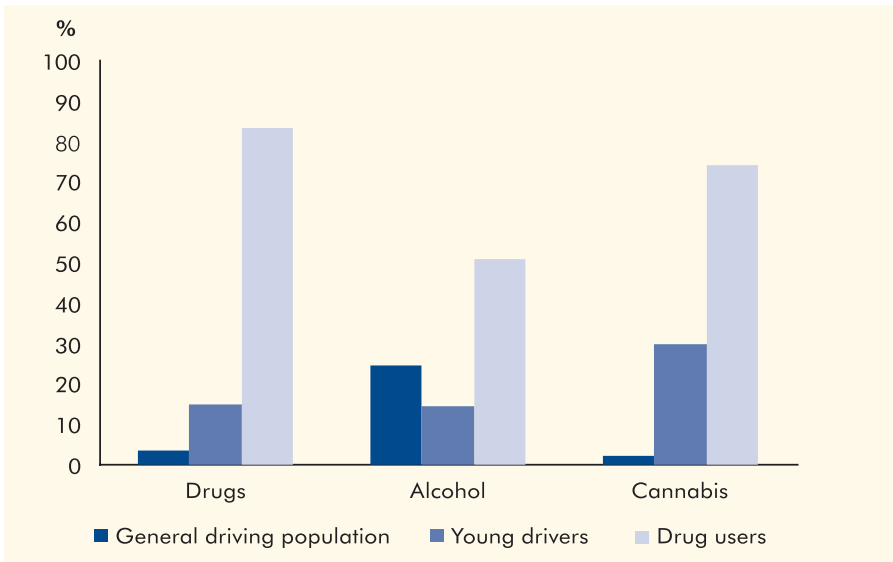
In this type of epidemiological study, a study population is surveyed using interviews or questionnaires about whether they have driven while under the influence of drugs or after the use of drugs. The results of nine surveys of the general population and the general driving population that have been published since 1999 are described in Table A7 (Appendix): two are from Australia (Australian Institute of Health and Welfare, 2001, 2004); three from Canada (Adlaf et al., 2003b; Beirness et al., 2003; Walsh and Mann, 1999); and one each from Denmark (Behrendorff and Steentoft, 2003); Spain (del Rio and Alvarez, 2001); the United Kingdom (Neale et al., 2000) and the United States (SAMHSA, 2006). Table A8 (Appendix) lists the results of eight surveys from 1999 or later of young drivers: three studies from Australia (Davey et al., 2005; Lenné et al., 2004; Lenton et al., 1999); two from Canada (Adlaf et al., 2003a; Asbridge et al., 2005); two from the United Kingdom (Neale et al., 2000; Terry and Wright, 2005) and one from the United States (SAMHSA, 2006).

The results of 10 surveys among drug users are described in Table A9 (Appendix). Published in 1999 or later, these include four studies from Australia (Aitken et al., 2000; Darke et al., 2004; Jones et al., 2005; Lenné et al., 2001), one from Canada (Walsh and Mann, 1999), one from Germany (Kubitzki, 2001), three from the United Kingdom (Albery et al., 2000; Neale et al., 2000; Terry and Wright, 2005) and one from the United States (Buchan et al., 2000).

From the survey data described in Tables A7–A9 in the Appendix, medians were calculated of the proportions of the various populations surveyed that report ever having driven under the influence of drugs, alcohol or cannabis (Figure 4).

About a quarter of the general driving population reports ever having driven under the influence of alcohol (25%, min.: 13%, max.: 64%). Driving under the influence of drugs is reported by about 3.4% (min.: 2.8%, max.: 4.3%) of the general driving population, and cannabis is the most frequently consumed drug (2.4%, min.: 1.5%, max.: 3%). Among young drivers, 14.6% (min.: 7.5%, max.: 69%) report ever having driven under the influence of alcohol and 15% (min.: 13.4%, max.: 25%) under the influence of drugs. Driving under the influence of cannabis is most frequently reported (30%, min.: 15.1%, max.: 59%) (7). The data from the surveys of drug users indicate that 83.5% (min.: 67.1%, max.: 94%) have ever driven a vehicle shortly after having

(7) The percentage of young drivers that reports driving under the influence of cannabis is higher than the percentage that reports driving under the influence of drugs. This is because the data that were used to calculate these percentages were not all from the same studies.



**Figure 4:** Median of the percentages of the general driving population, young drivers and drug users that report ever having driven under the influence of drugs, alcohol or cannabis (see Tables A7–A9 in the Appendix for survey details).

used drugs. About half of drug users have driven under the influence of alcohol (51 %, min.: 23 %, max.: 92 %). In a study in Germany, 92 % of young drug users said that they had driven under the influence of a combination of alcohol and drugs (Kubitzki, 2001). In a survey in Scotland of visitors to discos and nightclubs (Neale et al., 2000), the patterns of the respondents’ answers seem to be more in agreement with surveys of drug users than with surveys of young drivers.

## Conclusion

In Europe, the United States, Australia and Canada, about 1 % to 2 % of drivers stopped during roadside surveys, tested positive for drugs in saliva. One outlier was identified, namely a roadside survey in Scotland which found that about 11 % of the drivers tested positive for drugs in their saliva. Driving under the influence of a combination of alcohol and drugs is not uncommon. Not unexpectedly, higher prevalence rates were found in studies using urine samples (6.4–12 %) and in studies where samples were only collected on weekend nights (15 %). Studies conducted among drivers stopped on suspicion of alcohol or drug use or other subsets of drivers

usually find a higher prevalence rate of drugs than roadside surveys of general driving populations. The reason is the selection of drivers inherent to such subset surveys.

In drivers who were injured, killed or involved in a traffic accident, alcohol is more prevalent than any other psychoactive substance; illicit and medicinal drugs are also frequently detected, more often than in the general driving population (studies in Europe, the United States, South Africa, Canada and Hong Kong). Not all of the most common drug types are tested for. After alcohol, cannabis is the drug most commonly tested for, and the combination of alcohol and drugs is detected in a substantial number of samples. When samples were analysed for the presence of benzodiazepines, these substances were found in a substantial number of cases, and were sometimes even more prevalent than cannabis.

Among drivers stopped on suspicion of driving under the influence of drugs, a psychoactive substance other than alcohol is most frequently detected and, in most studies, it is cannabis. Drivers suspected of driving under the influence of alcohol are frequently also under the influence of drugs.

In surveys conducted by interview or questionnaire, driving under the influence of drugs is less frequently reported (about 3.4%) by the general driving population in seven countries than driving under the influence of alcohol (25%). In young drivers, on the other hand, the figures are similar for alcohol (14.6%) and drugs (15%). Cannabis is the drug most frequently reported by both the general driving population and young drivers. Among drug users, about 83% have ever driven a vehicle shortly after having used drugs. It is also worth noting that drug users often drive under the influence of alcohol.

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 1999, it can be concluded that driving under the influence of drugs is not uncommon and that it can cause a substantial risk to traffic safety.

A promising large-scale epidemiological study called DRUID (Driving under the influence of drugs, alcohol and medicines) was started in October 2006 and is expected to be completed in 2010 <sup>(8)</sup>. One of its aims is to analyse the prevalence of alcohol and other psychoactive substances in accidents and in the general driving population in 19 different European countries.

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<sup>(8)</sup> [www.druid-project.eu/clin\\_007/nn\\_107534/Druid/EN/home/](http://www.druid-project.eu/clin_007/nn_107534/Druid/EN/home/)







## Chapter 3: Effects and risks associated with drugs

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## 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, epidemiological 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. In small doses, cannabis

#### 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- $\Delta^9$ -THC and 8 $\beta$ -hydroxy- $\Delta^9$ -THC. The first is further metabolised to  $\Delta^9$ -THC-11-oic acid. Two inactive substances are also formed (8 $\alpha$ -hydroxy- $\Delta^9$ -THC and 8 $\alpha$ ,11-dihydroxy- $\Delta^9$ -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>).

produces euphoria, relief of anxiety, sedation and drowsiness. In some respects, the effects are similar to those caused by alcohol (9). 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). The 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; Kurzhthaler 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 THC's adverse effects.

A study by Ramaekers et al. (2006b) defined performance impairment (in terms of motor control, motor impulsivity and executive function) as a function of THC concentration in serum and oral fluid. The authors concluded that 2 and 5 ng/ml are the lower and upper ranges of a serum THC limit for impairment. Binomial tests showed an initial and significant shift toward impairment in the critical tracking task for 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.

Cannabis can also have an effect on behaviour. The effects of cannabis on risk-taking is, however, unclear. Laboratory experiments revealed an increased

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(9) See EMCDDA Drug profile, Cannabis (<http://www.emcdda.europa.eu/publications/drug-profiles/cannabis>).

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 are 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) were 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 are aware of the impairment and compensate their driving style by driving more slowly, overtaking less or keeping longer distances. However, they are still unable to compensate for the loss of capability in some psychomotor skills (Sexton et al., 2000, 2002). The experimental studies on cannabis traditionally used low-potency cannabis (maximum 4% THC). Other studies that have used high-potency cannabis (13% THC) show that impairment is more pronounced compared to the low-potency studies (see Chapter 1).

### **Duration of effects**

The desired effect of cannabis, the 'high', lasts for up to 2 hours (Couper and Logan, 2004b). However, most studies found significant negative effects of cannabis on performance up to 10 hours after use (Hart et al., 2001; Kurzhäler 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 had 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.

## Chronic effects

Chronic use of cannabis can lead to deficiencies in skills concerning 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.

## 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 Canada (Québec) showed that driving under the influence of cannabis alone was associated with an OR of 2.2 (95% CI: 1.5–3.4), while when all cannabis cases were taken into account, an OR of 4.6 (95% CI: 3.4–6.2) was found (Dussault et al., 2002). Driving under the influence of a combination of alcohol (BAC > 0.08%) 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 between 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), and with alcohol (BAC > 0.05%) plus cannabis, the increased risk was 4.6 (OR, 95% CI: 2.0–10.7). The Immortal study in the Netherlands and Norway showed 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 to 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 per 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 being responsible 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.

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 compared with non-users. There were no differences for women or former users.

In a case-control study, Blows et al. (2005) recorded drivers' self-reported cannabis use in the three hours prior to the crash or 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 drove under the influence of cannabis in the past year were over four times as likely as cannabis-free drivers to be involved in a motor vehicle collision, yet those who used the drug but did not drive while under its influence did not have an elevated accident risk.

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.

In the United Kingdom, results from a postal questionnaire survey showed 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).

### Responsibility analyses

A study conducted from 1990 to 1999 in 3 398 fatally injured drivers in Australia found an OR of 2.7 (95% CI: 1.02–7.0) for being responsible 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 positive for cannabis and with a BAC of 0.05% or higher compared with a BAC of 0.05% or higher and no cannabis use (OR 2.9, 95% CI: 1.1–7.7). In another study in Australia, conducted in 1995–96 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 for the combination of alcohol (BAC > 0.08%) and cannabis (OR 2.5, 95% CI: 0.3–20.2) (Dussault et al., 2002). In 10 748 drivers involved in fatal crashes in France from October 2001 to September 2003, positive cannabis detection 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 responsibility analyses in 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 due to 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 being positive for cannabis did 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).

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 through 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.

### Meta-analysis

We performed a meta-analysis<sup>(10)</sup> on the risk data for driving under the influence of cannabis alone. For the risk of being involved in a traffic accident, the data were based on the results from studies in France, the Netherlands and Norway (Assum et al., 2005; Mura et al., 2003). For the risk of being responsible for an accident, the data from four studies from Australia and the United States were used (Drummer et al., 2004; Longo et al., 2000b; Lowenstein and Koziol-McLain, 2001; Soderstrom et al., 2005). The results indicate a significantly increased risk of being involved in an accident (OR 3.0, 95% CI: 2.4–3.8; RR 2.2, 95% CI: 1.9–2.5), but no significant

<sup>(10)</sup> A meta-analysis is a statistical analysis of a large collection of analysis results from individual studies. The meta-analysis performed in this report was computed using the statistical programme MedCalc.

association between cannabis use and crash responsibility (OR 1.1, 95% CI: 0.8–1.6; RR 1.0, 95% CI: 0.9–1.2). Future research should investigate whether this might be due to the limitations inherent to responsibility analysis.

## 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 in 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 the decrements. The combined use 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.

A meta-analysis of the data from epidemiological studies has shown that cannabis use is associated with an increased risk of being involved in an accident, but not an increased risk of being responsible for an accident. One responsibility analysis, however, found an increased responsibility risk with increased cannabis concentration, indicating a possible causal relationship. Several studies found that the risk of being involved in or responsible for a traffic accident is higher for the combination of alcohol and cannabis than for cannabis or alcohol use alone.

## Opiates

Opiates can be divided into three groups, namely the opiates with morphine-like activity (for example, morphine, heroin, fentanyl and methadone), the opiates that block the activity of morphine and the opiates that exhibit mixed activity (for example, codeine, buprenorphine and pentazocine) (Drummer, 2001). In this report, the acute and chronic effects and risks associated with the following opiates will be discussed: morphine, heroin, methadone, buprenorphine and fentanyl.

Fishbain et al. (2003) conducted a structured, evidence-based review of whether the driving-related skills of opioid-dependent/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 motor vehicle violation

or motor vehicle accidents is not higher versus comparable controls. The analysis also revealed consistent evidence of no impairment 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 the studies in 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 have greater neuropsychological impairment than cocaine dependence/abuse addicts, who in turn will have greater impairment than controls.

## 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 to the effects of mixed-action opiates. They found that morphine decreased performance on the DSST test — 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 less magnitude than that caused by mixed-action opiates. 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 lorazepam (one of the comparator drugs in the study).

## **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 drug effects after ambulatory anaesthesia of propofol (2.5 mg/kg), propofol (2.0 mg/kg) and fentanyl (2 µg/kg), propofol (2.0 mg/kg) and midazolam (2 mg/70 kg) or midazolam (0.07 mg/kg) and fentanyl (2 µg/kg). Psychomotor function was impaired up to 2 hours after injection with each of the drug combinations. The multiple sleep latency test demonstrated sleepiness up to 8 hours after an injection of midazolam and fentanyl. Driving simulator tests, however, found no significant impairment at 2, 3 or 4 hours after a treatment with 2.5 mg/kg propofol and 1 µg/kg fentanyl (Sinclair et al., 2003).

## **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 range from 300 to 500 mg in addicts (Couper and Logan, 2004b). The effects of heroin on performance can last up to six 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 two hours after smoking and four 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  $\mu$ ,  $\kappa$  and  $\delta$  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 2–3 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  $\delta$ -monoacetylmorphine and slower conversion to morphine, the main active metabolite. The plasma half-life of diamorphine is about three minutes.

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

## Methadone

Several recent experimental studies have investigated the performance effects with substances used for substitution treatment. In a study of the acute effects of methadone in patients admitted to an opiate detoxification programme, patients were tested after three and five 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.

## 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 from the DSST showed no significant changes for any of the dose conditions tested, and no significant differences for 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 combination of intramuscular and sublingual buprenorphine and naloxone in opioid-dependent subjects, once given by intramuscular injection and once given sublingual. There was no evidence that sublingual buprenorphine and naloxone impair 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 percent errors. CLT performance was decreased with 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 of correctly identified targets significantly decreased.

## Chronic effects

### Opioid therapy

Larsen et al. (1999) compared attention and reaction time of patients on long-term opioid therapy (patients with cancer pain or chronic non-malignant pain) with 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 could be demonstrated between the three groups. However, in cancer patients, attention/concentration was more impaired

than in non-cancer patients taking opioids. Auditory and optical reaction times were significantly slower in patients on opioids than in the non-opioid analgesic group and highly significantly slower 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 had more similar ratings to the subjects in the control group who had failed rather than passed the evaluation. Sjogren et al. (2000b) 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 controls 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., 2000a). 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 taking chronic opioid therapy. The patients' results were worse on a concentration test and better on a coordination test than the results of healthy controls. The patients did not perform worse than healthy controls 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 controls. 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 eight 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 two weeks, on a series of computerised tests to measure attention, reaction, visual orientation, motor coordination and vigilance to the performance of healthy controls. None of the performance measures was significantly inferior in the group of patients compared to 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 re-administered at 90- and 180-day intervals (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 to their performance after being stabilised for one 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. (2006b), 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 the matched healthy controls, 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 controls. No significant effects were found in the laboratory tests.

### **Heroin dependence**

Chronic heroin use can have long-lasting effects on some cognitive and psychomotor skills. Studies have found an impairment of the 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 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 has 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 to 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 show cognitive deficits compared to 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 in 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 controls (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 controls in psychomotor speed, working memory, decision-making and meta-memory. 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 partially be caused by the heroin addiction instead of 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-opiate users and of matched controls 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-opiate users fell between that of the other two groups, without significant differences. Verdejo et al. (2005) also compared patients on methadone maintenance treatment patients 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 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 opiate-dependent subjects at baseline and after two 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-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. Results revealed little impairment in performance as the dose was increased four-fold (from 8/2 mg to 32/8 mg).

The only significant effect of dose was impairment in episodic/long-term memory performance at the highest dose, relative to the two lower doses.

Rogers et al. (1999) assessed decision-making in 13 opiate users, three of whom were currently using heroin and 10 were receiving methadone. The opiate users were found to deliberate significantly longer before making their choices than healthy volunteers. 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 controls 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 controls, whereas patients on methadone showed significantly prolonged mean decision and reaction times. A controlled clinical study also showed that buprenorphine produces partially 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 had more perseverative errors on the WCST compared with the control group whereas the buprenorphine group had intermediate scores. Scores on the WAIS-revised and the BVRT were similar for both opiate-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 0.05%). 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. (2005b) 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., 2005a).

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.

## 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.

Four epidemiological studies have investigated the risk of being involved in a traffic accident while driving under the influence of opiates. A case-control study in Canada showed that driving under the influence of opiates 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 found that use of codeine alone is not associated with an increased accident risk (RR 3.0, 95% CI: 0.7–14.2), while heroin and morphine alone are 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 opiates 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).

### Responsibility analyses

Three epidemiological studies studied the risk of being responsible for a traffic accident while driving under the influence of opiates. Drummer et al. (2004) found

that driving under the influence of opiates alone is not associated with an increased risk of being responsible for an accident (OR 1.4, 95% CI: 0.7–2.9). According to the authors, however, this does not mean that opiate use does not increase the risk of a driver being responsible for a crash. Because 65% of the opiate-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. Also, some drivers would have been tolerant to the effects of opiates and effectively misclassified as opiate-intoxicated, further reducing the study's ability to detect a real association between opiates and accident responsibility. Dussault et al. (2002) found that driving under the influence of opiates is associated with an infinite risk of being responsible for an accident. This is probably caused by the fact that of the limited number of fatally injured drivers testing positive for opiates, all drivers were judged responsible for the accident. In a study by Laumon et al. (2005), a blood concentration of opiates above 20 ng/ml was not associated with an increased risk of being responsible for a fatal accident (OR 0.9, 95% CI: 0.6–1.5); however, the OR was not adjusted for confounding factors.

### Meta-analysis

It was not possible to conduct a meta-analysis<sup>(11)</sup> on the data from the responsibility analyses. It was possible to conduct a meta-analysis on the data from the Immortal studies in Norway and the Netherlands that assessed the accident risk while driving under the influence of opiates alone (Assum et al., 2005). The results indicate that drivers under the influence of opiates alone are at increased risk of being involved in an accident, as indicated by RR of 3.2 (95% CI: 1.4–6.9) and an OR of 3.7 (95% CI: 1.4–10.0).

### Conclusion

Opiates acutely cause some cognitive and psychomotor impairment, but these are highly dependent on the type of opiate and the dose administered. The effects are mostly moderate. Morphine tends to slow users' responses, though accuracy is not diminished. Fentanyl produces cognitive impairment in doses common in out-patient surgical procedures, but shows little impairment effect when used for longer-term pain management. With use of heroin, severe impairment can be expected; however,

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<sup>(11)</sup> A meta-analysis is a statistical analysis of a large collection of analysis results from individual studies. The meta-analysis performed in this report was computed using the statistical programme MedCalc.

no recent experimental studies have been conducted using doses that approximate realistic doses. 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. Some of the impairments are related to the severity of dependence and the duration of use. Acute effects of methadone can be avoided by dividing the daily dose. Methadone maintenance treatment does cause impairment, including additional impairment over and above that associated with heroin dependence, though this latter can in some cases be better explained by other associated risk factors. The results of one study suggest that impairment caused by methadone maintenance treatment may be reversible. Buprenorphine users have not generally shown impairment, except at high doses.

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 taking 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 limited epidemiological studies demonstrate inconclusive evidence on the accident risk associated with opiate use. Some studies found significantly elevated accident risks associated with driving under the influence of opiates. Two out of three responsibility analyses found no increased risk of being responsible for an accident while under the influence of opiates, whereas the third found that opiates were associated with an infinite risk of being responsible for a traffic accident. Future studies should investigate whether this could be because of the limitations inherent to the responsibility analyses.

## 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 following experimental studies were very low (10–30 mg) and thus not representative of realistic situations (100–1 000 mg/day) (Couper and Logan, 2004b).

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

## Pharmacology of amphetamine

Amphetamine is a central nervous system 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 <sup>(12)</sup> on performance on neurocognitive measures by non-fatigued healthy adults found varying results. McKein 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

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<sup>(12)</sup> Dextroamphetamine is the *d* form of amphetamine (which is more active than the *l* form). For more details, the reader can refer to: <http://www.emcdda.europa.eu/publications/drug-profiles/amphetamine>



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 showed a decrease in several forms of impulsive behaviour, while alcohol (0.2, 0.4 and 0.8 g/l) showed 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 only observed during the daytime, which is consistent with the tunnel vision that is associated with amphetamine consumption (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 (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 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 with performances at the 13.00 pre-drug baseline session, showed that dextroamphetamine improved performance at both post-drug sessions for all tasks in which subjects had shown impairment due to sleep deprivation — except one task. The exception was in logical reasoning 1.5 hours post-drug administration. However, this effect was significantly improved 5.5 hours after dextroamphetamine administration.

Jones and Holmgren (2005) presented a case series of individuals apprehended in Sweden for DUID 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.

## Methamphetamine

In healthy volunteers, Comer et al. (2001) found no effect of 5 or 10 mg methamphetamine on 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<sup>(13)</sup> (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 percent correct/time ratio. There was no effect on FTT, a measure of motor speed. The same research group

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<sup>(13)</sup> There are three different types of methamphetamine (*d*, *d/l* and *l*) and each affects the central nervous system differently. The most common types are the dextro/levo (*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 central nervous system 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 nine 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>).

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).

## MDMA

Laboratory studies have variously shown negative, 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 euphoria in the Maddox wing device. Hernandez-

## 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 two 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>).

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 euphoria in the Maddox wing device. In a study in 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 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 to 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 shortly after the use of MDMA, before going to a party, and then again while sober on a control night at a comparable time. Under the influence of MDMA, subjects drove faster, but only in the built-up area with a speed limit of 50 km/h. Speed variance increased as well, both in the city and on the motorway. Lateral control and gap acceptance behaviour was not affected. Crashes occurred during two of the 20 control rides, and four times while under the influence of MDMA, a 100% increase.

In another study in recreational MDMA users, subjects took a real on-the-road driving test three to five hours after use of 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 used by recreational MDMA users (average: 120 mg) (Couper and Logan, 2004b).

### **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 reverted the exophoria induced by alcohol in the Maddox wing test. SRT was significantly increased for the combination of MDMA and alcohol, but not for 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 a comparable time at 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 decreased sense for risk taking, 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 or even causation 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‰), while other negative effects of alcohol can be reinforced.

### **Duration of effects of amphetamines**

Effects on cognitive and psychomotor skills have been assessed for up to three to four hours after administration of amphetamine (Asgar 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). With MDMA use, the duration of the subjective 'positive' effects is less than 24 hours, but 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 five hours (Lamers et al., 2003). The duration of the cognitive effects is unclear. Some studies show that the negative effects on cognitive performance, especially verbal memory, can last for several days (Smith et al. 2006), while others found that impairments disappear after a few hours (Farré et al., 2004) or 24 hours after 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 up to two years since 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 at the Norwegian Institute of Public Health. In each case, the police physician had determined whether the driver was impaired or not; 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 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).

## Responsibility analyses

Four epidemiological studies evaluated the risk of being responsible for an accident while driving under the influence of amphetamines, including two in Australia. In one

of these, Drummer et al. (2004) conducted a responsibility analysis in 3 398 fatally injured drivers. They did not calculate the risks associated 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 being responsible 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 being responsible for an accident (3.8 OR, 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 (2.0 OR, 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 through 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**

There were insufficient data to conduct a meta-analysis on the risk of being involved in or responsible for an accident while driving under the influence of amphetamines.



## Conclusion

Experimental studies show that methamphetamine and amphetamine can cause 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. However, the doses used in these studies are not representative for the doses actually consumed by users of these drugs.

Experimental studies of MDMA 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. Other psychoactive substances such as alcohol can reinforce the deleterious effects of MDMA, and even cause some additional negative effects. The use of MDMA can diminish some, but not all, deleterious effects of alcohol, while other negative effects of alcohol can be reinforced.

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

Epidemiological data on the risks associated with the use of amphetamines are rare. Results from one out of four available studies on accident involvement indicate that amphetamines are associated with an increased risk of involvement in an accident. In the amphetamine studies that investigated responsibility, no significant increased risk of being responsible for an accident was found. A study of drivers involved in accidents while under the influence of amphetamines found no association between the use of the drugs and the severity of the accident.

## Cocaine

### Acute effects

Only two recent experimental studies were found on the acute effects of cocaine on performance. 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 DSST was assessed before drug administration and periodically afterwards for five 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

## 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>).*

reported substantially less cocaine use than the subjects in their own study, who may have developed tolerance to cocaine's performance-enhancing effects. Furthermore, the route of administration was oral in their own study (producing less 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 conclude 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.

## 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 to 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 HCl) 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 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)

(Dussault et al., 2002). Driving under the influence of cocaine alone, a combination of cocaine and cannabis, a combination of cocaine and alcohol (BAC > 0.8 ‰), or a combination of cocaine, cannabis and alcohol (BAC > 0.8 ‰) was associated with an increased accident risk of respectively 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).

### Responsibility analyses

Four accident responsibility analyses were found for driving under the influence of cocaine. Drummer et al. (2004), in their responsibility analysis of 3398 fatally injured drivers, did not calculate the risks associated with driving under the influence of cocaine alone, but 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 being responsible for an accident. This is probably because only a limited number of fatally injured drivers tested positive for cocaine and that 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 being responsible for an accident (4.4 OR, 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 (4.2 OR, 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 (2.3 OR, 95% CI: 1.4–4.0).

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 that 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

There were insufficient data available to conduct a meta-analysis on the studies of cocaine use and the risk of being involved in, or responsible for an accident.

## Conclusion

Few 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.

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.

Epidemiological studies show that cocaine may increase the risk of being involved in or responsible for an accident. Accident risk is higher when cocaine is used in combination with another psychoactive substance, such as alcohol and/or cannabis.

## 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. clonazepam). Benzodiazepines bind to the GABAA receptor 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 only exert 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; they can be quite severe, especially with the short- and medium-acting substances.

The newer benzodiazepine-like drugs (zolpidem, zaleplon and zopiclone) were thought less likely to lead to dependence, although recent evidence suggests that there may be no difference with the benzodiazepines.

## Effects

Table A10 (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 two to five hours before awakening. A battery of tests (including CRT, DSST, CFF and LARS) were conducted 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 five 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 after 1.25 hours and 8.25 hours with 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 for zolpidem 20 mg and triazolam 0.25 mg.

Hindmarch et al. (2001b) administered zolpidem (10 mg) or zaleplon (10 or 20 mg) at night-time, 5, 3 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 one 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 up to three hours following administration, and effect on CRT and delayed free recall of words that lasted up to five hours after administration. Zolpidem 10 mg showed more residual effects than zaleplon 20 mg.

In another night-time-administration study, Verster et al. (2002b) 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 one 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 four 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 (one hour after dose administration), and no impairment of driving abilities when measured four 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 the EEG and the DSST. The changes for the measures are highly correlated.

Vermeeren et al. (2002b) 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.

### ***Medium-acting benzodiazepines***

#### *Alprazolam*

Mills et al. (2001) studied the effects of stimulants and sedatives on tunnel vision. The study was with fully rested participants: alprazolam (0.5 mg) clearly impaired performance while stimulants (dextroamphetamine 10 mg) enhanced performance.

Verster et al. (2002a) 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. Also, 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 (2004b) 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 (XR) and 1 mg alprazolam immediate release (IR). Four hours post-dosing, a standardised driving test was performed, cognitive and psychomotor tests were performed 2.5 and 5.5 hours post-dosing, and memory function was assessed one hour after administration. Severe impairment of driving performance was noted. Impairment with the XR formulation was only half of that observed with the IR 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.

### *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 seven days. Tests included EEG recording, sleep latency test, driving test (SDLP) and subjective assessments. With lorazepam, marked impairment on the driving test and 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 lorazepam-positive driving cases. When lorazepam alone caused the impairment, significant psychomotor disability was established that was independent of blood concentration (range: 0.01–0.13 mg/l).

A study by Soo-ampon et al. (2004) on the effects on recall memory of lorazepam 2 mg alone, alcohol 0.6 g/l alone or the two combined showed that word frequency had a significant impact on memory. 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 three 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 to 30 mg) in older adults. Those that were observed were in the areas of affective/behavioural/cognitive function, neuro-sensory 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 four hours following intake, while clonazepam (3 mg) affected memory and attention for 6 hours and reduced psychomotor performance two 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 a hidden belonging at the end of the session. Diazepam impaired performance on all measures.

### *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 in the first part of the morning, while zolpidem was free of any effect. Also, flunitrazepam and zopiclone affected eye movements 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 expectancies and rated their own performance more negatively.

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 showed clear impairment, even with low amounts of alcohol.

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 between either zolpidem or temazepam compared to placebo were observed, 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 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, while an impairment for the LMT with lormetazepam was observed.

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 incomplete 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 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 an EEG and a driving simulation test 9 to 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 as tested using the SRT, logical reasoning task, serial subtraction task and multitask. Time to normal recovery on the SRT for zaleplon, zopiclone and temazepam were 3.25 hours, 6.25 hours and 5.25 hours, respectively.

## 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 compared with the subjects who were not impaired. There was a clear concentration-related effect of benzodiazepines on performance.

## Accident risk

Four epidemiological studies were found that investigated the risk of being involved in a traffic accident after having taken a benzodiazepine. 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 > 0.08%) was associated with an infinite risk of being involved in a traffic accident, but this is probably due to the limited number of drivers testing positive for this combination. A comparison of the prevalence of alcohol, drugs and medicines between 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 recent pharmacoepidemiological study was found that investigated the relationship between responsibility for a traffic accident and benzodiazepine use in the elderly (McGwin et al., 2000). The results showed that the use of benzodiazepines was not associated with an increased risk of being responsible 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).

### Responsibility analyses

Three responsibility analyses were found on benzodiazepines and accident responsibility. In Australia, a study on alcohol and drug use in 3 398 fatally injured drivers indicated that drivers testing positive for benzodiazepines did not have an increased risk of being responsible for an 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 in 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 being responsible 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 use of a combination of benzodiazepines and cannabis because all drivers testing positive for this combination were judged responsible. A responsibility analysis in Canada in 482 fatally injured drivers found that drivers testing positive for benzodiazepines, or for benzodiazepines alone, had no higher risk of being responsible 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 > 0.08%) 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.

### **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 testing 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 a increasing but non-significant accident risk (OR 1.5, 95% CI: 0.9–2.4; RR 1.1, 95% CI: 1.0–1.3).

### **Conclusion**

Benzodiazepines 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 little impairing effects (though some for 20 mg doses), whereas zolpidem and zopiclone, and to some extent triazolam do produce impairment. Among the intermediate-acting benzodiazepines, alprazolam and lorazepam cause marked impairment, and less so for lormetazepam and temazepam. The limited studies using long-acting benzodiazepines showed impairment for flunitrazepam, clonazepam and diazepam.

From the data collected, it seems 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. Combination with alcohol showed clear impairment for temazepam, lorazepam and triazolam. 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. It should also be noted that with chronic and subchronic use, tolerance may develop, partially or completely, to the impairing effects.

Epidemiological studies indicate that drivers have an increased risk of being involved in a traffic accident after having taken a benzodiazepine, though no distinction was made between the different kinds of benzodiazepines. Results from responsibility analyses are contradictory. Only one study (out of the three found) showed that drivers testing positive for benzodiazepines are at an increased risk of being responsible for an accident, and that the risk rises with increased concentrations of

benzodiazepines. But what is clear from all the risk analyses on benzodiazepines is that 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.

## 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 vasodilatation, 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, digestive tract troubles and anticholinergic effects. The antihistamines discussed here are  $H_1$ -receptor antagonists, although sometimes affinities for other histamine receptors (sometimes acting as agonists rather than antagonists) or muscarinergic, adrenergic or serotonergic receptors as well as cardiac ion channels (calcium and potassium) occur — 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 2). 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 CYP3A4 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



**Table 2: Overview of the different types of antihistamines**

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

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

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 improved alertness that results from the drug's histamine 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 A11 (Appendix).

### ***First-generation antihistamines***

#### *Diphenhydramine*

Tolerance to the sedative effects of antihistamines was studied by Richardson et al. (2002). Diphenhydramine 50 mg given twice daily for four days showed almost

complete reversal of the impairment of performance compared with placebo. Tolerance was complete by the end of three days of administration.

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 *bid* versus dexchlorpheniramine 6 mg, chlorpheniramine 4 mg *bid*, brompheniramine 12 mg *bid* and hydroxyzine 25 mg *bid* 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. (2006b) compared the effects of mequitazine 5, 10 or 15 mg to 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. Divided attention was also affected as was the reaction time (dose-related). Dexchlorpheniramine impaired driving performance, as indicated by a significant rise in SDLP. It was concluded that mequitazine was mildly sedating.

### *Chlorpheniramine*

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

Chlorpheniramine has major adverse effects on the central nervous system. 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, for example, found that the use of dexchlorpheniramine 4 mg can lead to auditory attention impairment, but that there is a lack of awareness of these side-effects by patients (Serra-Grabulosa et al., 2001).

### *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 showed evidence of impairment.

A study of antivertiginous medications by Philipova et al. (2004) found no evidence of impairment of reaction time after four doses in 24 hours of cinnarizine 20 mg or dimenhydrinate 40 mg.

Another study of antivertiginous medications by Schneider et al. (2003) found also 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 is free of daytime sleep latencies, adverse effects on psychomotor performance and subjective sleepiness. The study was a cross-over design with promethazine as an active control. Assessments were made one hour before and from 0.5 to 8 hours post-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 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 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 8000 feet (about 2400 m) altitude, desloratadine 5 mg, diphenhydramine 50 mg and placebo, all in single doses on different days with 7-day wash-out 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 were 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 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, except the incidence of somnolence, which 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) in comparison with 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 showed no difference in adverse event rates, including that for somnolence, which was as high as 9.6% for the subjects who received cetirizine (Martínez-Cócerca 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 compared to those taking emedastine 2 or 4 mg *bid* (Vermeeren et al., 2002a). 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 cross-over, double-blind study (Hindmarch et al., 2002). The test battery consisted of CFF, CRT, 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. (2006a) investigated whether this was due to 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<sub>3</sub> receptors and/or GABA receptors.

In a study by Ridout et al. (2003b), 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, with the conclusion that the incidence of adverse events was low.

### *Azelastine*

The effects 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) showed no significant impairment associated with fexofenadine use relative to placebo, whereas cetirizine use showed a trend towards 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 *bid*, cetirizine 10 mg, fexofenadine 60 mg *bid* and olopatadine 5 mg *bid* on wheal-and flare-response, sedation and psychomotor performance. The visual analogue scale was used to test for sedation and a word processor test was used to test psychomotor activity. Olopatadine, fexofenadine and cetirizine showed a significant sedative effect in this order, while bepotastine showed the least. Olopatadine affected psychomotor performance more markedly, followed by fexofenadine and cetirizine.

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

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

Inter-drug differences in sedation caused by antihistamines is discussed by Shamsi and Hindmarch (2000). They used proportional impairment ratios for objective evidence (PIR-O) for ranking 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 of no impairment, while promethazine ranked the lowest.

A prescription-event monitoring study showed an overall low incidence of sedation for four second-generation antihistamines (cetirizine, fexofenadine, loratadine and acrivastine) (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 are 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 with high doses, which showed small effects. Fexofenadine was free of sedative effects at any dose.

Fexofenadine 120 mg, compared to hydroxyzine 30 mg had no influence on BRT when driving and using a mobile phone, while hydroxyzine did slow down 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 (TOVA) 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 than 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) showed that desloratadine improved ragweed-induced allergic rhinitis symptoms 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 smaller 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 a wearing off of the driving impairment after eight days (Theunissen et al., 2006b). 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., 2003b). 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., 2003a). 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 two hours post-dosing. No significant effect of desloratadine on SDLP was noted (while 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 diphenhydramine and second-generation antihistamines studies did not find consistent diphenhydramine-induced sedation. They 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 fexofenadine 60 mg, diphenhydramine 50 mg and alcohol 1 g/l (BAC) versus placebo. Driving performance was assessed with a 1-hour driving simulation. Fexofenadine and placebo had equal effects, while diphenhydramine had an even greater impact on driving performance than alcohol.

An analysis by Verster and Volkerts (2004a) shows significant impairment associated with the use of first-generation antihistamines, 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 time between testing and administration. The second generation antihistamines fexofenadine and levocetirizine produce no driving impairment.

Hindmarch et al. (2001a) 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.

## Risks

### *Accident risk*

No recent epidemiological studies were found that specifically investigated the accident risk associated with antihistamines. Some studies, however, 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 being responsible for a traffic accident while under the influence of psychoactive drugs, including sedating antihistamines, but also TCA, 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 being responsible for a traffic accident (3.8 OR, 95% CI: 1.3–11).

## Conclusion

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 sedating effects. Tolerance to the effects seems to be the case with repeated use of diphenhydramine, mequitazine and dexchlorpheniramine.

Among the drugs of the second generation, fexofenadine, even at high doses, is not associated with impairment, as is also the case with ebastine. Desloratadine and loratadine are free of any disruptive effects on psychomotor performance, nor do they 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. Alcohol can have an additive effect on antihistamines' sedation and psychomotor impairments. Fexofenadine does not potentiate the effects of alcohol and vice versa.

The antihistamines that do not cause impairment should be preferred for prescription to drivers. Based on the studies discussed above, it seems that fexofenadine,

desloratadine and ebastine are the safest options to be used. Also, topical azelastine does not appear to have an effect on vigilance.

More epidemiological research is needed on the risks of being involved in or responsible for a traffic accident that are associated with antihistamine use.

## 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 3). The second-generation drugs are associated with fewer adverse effects compared to 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), sedation (with the serotonergic compounds), while second-generation selective serotonin reuptake inhibitors (SSRIs) are more prone to causing gastrointestinal disturbances and sexual dysfunction.

### Acute effects

Table A12 (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 a clear impairment associated with these substances. According to the ICADTS classification (<sup>14</sup>), 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 comprise memory (measured by MMSE) over a substantial timespan.

Veldhuijzen et al. (2006a) 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

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<sup>14</sup> <http://www.icadts.org/reports/medicinaldrugs1.pdf> and <http://www.icadts.nl/reports/medicinaldrugs2.pdf> for the list of drugs.

**Table 3: Overview of the different kinds of antidepressants**

Class	Mechanism of action	Examples
First generation (TCA)	Noradrenergic	Nortriptyline, desipramine, protriptyline, maprotiline, amoxapine
	Serotonergic	Amitriptyline, clomipramine, doxepin, imipramine, trimipramine, dosulepine, melitracen
Second generation	SSRI	Paroxetine, sertraline, citalopram, escitalopram, fluvoxamine, fluoxetine
	NRI	Reboxetine, atomoxetine
	SNRI	Venlafaxine, milnacipran, duloxetine
Atypical		Trazodone, nefazodone, bupropion, mianserin/mirtazapine, tianeptine/amineptine
MAO inhibitors		Selegiline (MAOI-B), phenelzine (MAOI-A), tranylcypromine (MAOI-A), moclobemide (RIMA)

Abbreviations: SSRI, selective serotonin-reuptake inhibitor; SNRI, serotonin/norepinephrine-reuptake inhibitor; NRI, norepinephrine-reuptake inhibitor; MAOI, monoamine oxidase inhibitor; RIMA, reversible inhibitor of MAOI-A.

was noted, higher than with a BAC of 0.5 g/l. Also, reaction times increased significantly. In contrast, after two weeks of treatment, no differences were found compared to placebo, suggesting tolerance.

### **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 show acceleration in 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 nine weeks of treatment (Strik et al., 2006).

SSRIs do not always show an improvement of memory 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 one week of treatment, whereas a study by Devanand et al. (2003) found little improvement of 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 of 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), only discontinuation of paroxetine, and no 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). Results showed an improvement on the SDLP test during SSRI use (6–52 weeks). However, performance was still significantly worse than that of the healthy controls. As for cognitive function, there was no significant difference in performance between healthy individuals and those taking antidepressants, except for the reduction of the CFF threshold in the subjects taking antidepressants.

### SNRIs

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, lengthened CRT and increased the errors in compensatory tracking. Poirier et al. (2004) tested the effect of milnacipran on memory and vigilance (CFF, 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 *bid* 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 *bid* does not affect the psychomotor functions required for driving. The drug did not accentuate the negative effects of alcohol.

### ***Within-generation comparisons***

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

A comparison between SSRIs (sertraline, paroxetine, citalopram) and SNRIs (venlafaxine) shows an impaired driving performance (on SDLP and CFF) for both classes of antidepressants (Wingen et al., 2006b). However, the authors remarked that this impairment is probably due to residual depressive symptoms.

### ***Comparison between generations***

#### *Driving performance*

The effects on driving performance with use of TCAs and SSRIs are summarised in a review by Ramaekers (2003a). SDLP during a one-hour on-the-road driving test was assessed. Sedating antidepressants (TCAs and mianserin) led to a change in SDLP similar to that 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. (2003a) 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 controls. 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 four 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 compared to 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 imipramine 50–100 mg administration 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 for fluoxetine and sertraline, while TCAs decreased the CFF threshold. Paroxetine produced no impairment of performance compared to 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 sometimes this is 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 of cognitive function and an improvement of the symptoms of the depression with use of sertraline 50 mg, fluoxetine 20 mg or nortriptyline 25 mg. Venlafaxine (37.5 mg *bid*) compared to 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. (2006a), 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.

### ***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 *bid* does not appear to affect cognitive function (Siepmann et al., 2004). The tests included CFF, CRT and memory.

## Risks

### **Accident involvement**

Two epidemiological studies were found that investigated the accident risk associated with antidepressant use. 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 controls.

### **Responsibility analyses**

One responsibility analysis was found that calculated the risk of being responsible 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 being responsible for a traffic accident (3.8 OR, 95% CI: 1.3–11) (Drummer et al., 2004).

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 being responsible 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 for a traffic accident (Barbone et al., 1998).

## Conclusion

Moclobemide, tianeptine, the SNRIs venlafaxine and milnacipran and the SSRI escitalopram seem to cause no major impairment of cognition or psychomotor skills. Withdrawal symptoms with venlafaxine or paroxetine can cause serious impairment. Mirtazapine use leads to clear impairment of memory, but subjects who took the drug before bedtime did not fail a driving test the next morning. TCAs, compared with the more recent antidepressants, show more impairment of cognition and psychomotor skills. However, tolerance to the cognitive and psychomotor effects of TCA seems to develop with prolonged use. Nevertheless, caution should be advised when prescribing these older substances, since previous studies clearly demonstrate an impairing effect. The results of the SSRI studies are not always consistent. Sertraline use was associated with improvement of psychomotor function. For most SSRIs, cognitive function was either unchanged or improved. 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.

The epidemiological data on the risks associated with antidepressant use do not indicate an increased risk of being involved in or responsible for an accident. However, very few data were available.

## Other synthetic drugs

### Gamma-hydroxybutyrate (GHB)

Gamma-hydroxybutyrate (GHB) is a normal component of the mammalian central nervous system. In the 1960s, synthetic GHB began to be used as an anaesthetic. 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 (FDA) removed GHB from the market in 1990 following reports of GHB-related coma and seizures (Freese et al., 2002). GHB (Xyrem™) has recently been approved in Europe for the treatment of narcolepsy <sup>(15)</sup>.

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<sup>(15)</sup> <http://www.marketwire.com/press-release/ucb-bxs-ucb.br-721758.html>

## Acute effects

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

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.

Haller et al. (2004) administered 50 mg/kg GHB to 8 healthy adults, 0.6 g/l ethanol in two doses or both drugs in a double-blind, placebo-controlled, four-arm crossover study. 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 suprathreshold doses of GHB (2–18 g/70 kg) and compared them to 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. Also, 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 concentrations were 79.1, 83.1, 113.5 and 130.1 mg/l for the doses of 40, 50, 60 and 72 mg/kg, respectively. GHB showed a mixed stimulant-sedative pattern, with initially increased scores in 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 of psychomotor performance that was apparently dose-dependent with a peak effect at 30 minutes after administration for lower doses, and at 1.5 hours post-administration for the 72 mg/kg dose. A decrease was seen in DSST total responses and DSST correct responses, while there was an increase in DSST errors at the same time. Doses of 60 and 72 mg/kg were associated with an impairment of the balance task with a peak effect at one hour, post-administration.

At all administered doses, GHB induced exophoria, a typical effect for 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) describe 13 subjects arrested for impaired driving in the United States whose blood samples were 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 eight-month period for driving under the influence of GHB (Couper and Logan, 2004a). 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 travel, 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 present in the subject's blood (thiopental and diazepam) that may also have contributed to the observed driving impairment.

Bosman and Luthof (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 2000 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.

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

## Conclusion

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) (Abanades et al., 2006) can cause dose-dependent cognitive and psychomotor impairments. The results from case reports also indicate impairments following GHB use by drivers, including extreme

sleepiness, poor coordination and balance and even unconsciousness. No risk studies were found.

## **Ketamine**

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

### **Acute effects**

Several experimental studies were found that assessed the acute effects of ketamine. Curran and Morgan (2000) investigated the cognitive effects of ketamine in recreational users on the night of drug use and three 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 for 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 ( $\pm 0.16$  g). The ketamine users were profoundly impaired on virtually all objective assessments of cognitive function, compared to the controls on the day they took the drug. On most objective measures, ketamine users performed at much higher levels on day three than day 0. However, on certain measures, group differences were still highly significant on day three, 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/hour) 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 one 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/hour) or placebo during two test days separated by approximately one week. In the first study, subjects reduced the number of total and perseverative errors with a single repetition of the WCST. In the second study, ketamine significantly increased

the number of total errors and the number and percent 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 on 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 slowed down 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) and a high ketamine dose (target plasma concentration 100 ng/ml). Impairments were seen only at the higher dose of ketamine and 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 ketamine produced a significant impairment in the manipulation of information within working memory.

Morgan et al. (2004b) 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 three days after administration (Morgan et al., 2004a).

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 remaining extent 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 five minutes for the low- and the high-dose conditions, followed by infusion with 0.003 mg/kg/minute for the low dose and 0.005 mg/kg/minute for the high dose) on neuropsychological tests in healthy male volunteers. Results indicated that both doses produce only nonsignificant 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) in 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. Whereas impairment on most of the psychomotor measures dissipated within two hours of injection, performance on the CLT and subjective feelings of alertness, drug liking-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.

### ***Combination with other psychoactive substances***

Krystal et al. (2005) investigated the effects of administering ketamine (one-minute infusion of 0.23 mg/kg followed by a one-hour infusion of 0.5 mg/kg) combined with amphetamine (one-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 0.65 mg/kg/hour). 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 three 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 three days later. On day three, 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., 2004d, 2006b). During a three-year longitudinal investigation of the cognitive and subjective effects of ketamine in recreational users who have substantially reduced their use of the drug, Morgan et al. (2004c) found that semantic memory impairments associated with recreational ketamine were reversible upon marked reduction of use. However, impairments to episodic memory and possibly attentional functioning appeared 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

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, while other functions, such as semantic memory, are not affected. Some of these defects are dose-dependent and can be attenuated by, for example, amphetamine or nicotine. Recreational use of ketamine can cause cognitive defects, of which some are reversible and others long-lasting.

No studies were found on accident risks associated with the use of ketamine.

### Phencyclidine (PCP)

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 were found that were published in 1999 or later. Studies that were published before 1999 showed that a

single dose of PCP, in subanaesthetic doses (<20 mg), can induce severe impairment of cognitive and psychomotor functions lasting up to 14 hours in healthy volunteers (Baselt, 2001).

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

## 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, decongestant and to treat 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  $\beta$ -adrenergic antagonist), 25 mg of ephedrine (a  $\beta$ -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 compared with 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  $\alpha_2$ -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 were found on the chronic effects of ephedrine.

### **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 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 being responsible 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 15.30 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 13.00 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

There were no studies found that examined the accident risks associated with phentermine, specifically. However, two responsibility analyses were found that investigated the risk of being responsible 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 risk of being responsible for an accident.

## 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. Amphetamine and methamphetamine may cause positive stimulating effects on cognitive and psychomotor functions, especially in fatigued or sleep-deprived individuals; however, negative effects are also observed with the use of these drugs, including an overall decreased driving capacity seen in driving simulator tests that approximate daytime conditions. Experimental studies on MDMA also found both negative and positive effects on performance. Numerous studies on the opiates 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 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. 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 (for instance, cannabis) with alcohol can cause impairment in addition to that caused by either substance alone, while other illicit drugs (for example, 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 cocaine's acute effects, 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

tricyclic antidepressants. Nevertheless, in every therapeutic class, some substances have been associated with little or no impairment, and these should preferably be prescribed to drivers.

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 may develop, partially or completely, to the impairing effects that have been observed for some benzodiazepines. Based on the studies on antihistamines, it seems that fexofenadine, desloratadine and ebastine (which are second-generation antihistamines of the class piperidines) are the least impairing options. Fexofenadine in particular, in contrast to the other drugs, does not potentiate the effects of alcohol or vice versa. Also, the use of topical azelastine (second generation, class phtalazinones) does not appear to affect vigilance.

Experimental data on antidepressants show that tricyclic antidepressants (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.

Epidemiological studies also suggest that driving ability is impaired by many illicit drugs. Increased accident risk and/or risk of being responsible for an accident were found for cannabis, amphetamines, heroin and cocaine, and many of these risks increase when the drug is consumed with another psychoactive substance, such as alcohol. Epidemiological data on the accident risks associated with therapeutic drugs are rare. For benzodiazepines, however, some studies clearly indicate an increased accident risk and an increased risk of being responsible for an accident.

These are useful findings but they come with various limitations. The DRUID project is therefore promising, as this European consortium will conduct reference studies on the effects of alcohol, illicit drugs and psychoactive medicines on driving ability, and it will also calculate detection and risk thresholds for several illicit and licit drugs.



## Overall conclusion

The use of illicit drugs in the EU as reported by the EMCDDA has, as a whole, increased since the late 1990s. It is perhaps not surprising then that the prevalence estimates of drivers under the influence of drugs on EU roads seem to have greatly increased during the same period. Comparisons are extremely difficult to make because of the considerable changes in statistics collection between then and now, but both 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. The range of psychoactive substances available for illicit use is widening, and the latest studies which look for evidence of their use in drivers are indeed finding it. Drivers are being discovered with a range of drugs in various subsets of the motoring population, whether while being tested randomly, upon suspicion, in hospital or after a fatal accident.

This report aims to add to the knowledge accumulated in the 1999 literature review (EMCDDA, 1999), 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. According to new guidelines for research into drugs and driving (NIDA, 2007), comparisons of such cases should take into account the different study designs, biological matrices tested, cut-off levels, etc.

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, where drivers were tested only on suspicion, cannabis was the most prevalent. Even in questionnaire surveys of drivers, they report having driven under the influence of drugs — again, mainly cannabis.

Most illicit drugs can have an effect on varying aspects of driving performance. Some dose-dependent impairment has been shown, but only for 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, due to tunnel vision. Experimental studies with low or medium doses of MDMA showed no impairment, or even improvement, of 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 opiates 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, but 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. Tricyclic antidepressants show 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.

New studies have been published since the end of 2006 that are not discussed in detail in this report, and the DRUID project aims to deliver more authoritative results in 2010, but it is already clear that driving under the influence of illicit or medicinal drugs is not uncommon and can cause a substantial risk to traffic safety. Nevertheless, at this early stage, policy responses already implemented are encountering numerous challenges to their effectiveness.

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 enough to have the correct effect but not enough to lose driving skills or ability, something that could seriously affect the patient's quality of life. Roadside detection mechanisms, whether traffic police with special training, or testing of drivers' biological samples, continue to suffer accuracy concerns, with even the newer technological advances not being considered reliable enough by an international testing project to be recommended for use in EU countries <sup>(16)</sup>.

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

In addition, it is difficult to apply the BAC parallel to 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 such a 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

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<sup>(16)</sup> Rosita project (<http://www.rosita.org>).

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.

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 only give rise to more questions. Nevertheless, the EMCDDA aims to give a more accurate delimitation of the problem to date in this fast-moving area of research, to assist policymakers to choose more effective solutions for their countries, as we wait for DRUID to report in a few years' time.



## Abbreviations

11-OH-THC	11-hydroxy- $\Delta^9$ -tetrahydrocannabinol
BAC	Blood alcohol concentration
<i>bid</i>	<i>Bis in die</i> (twice a day)
BRT	Brake reaction time
BVRT	Benton visual retention test
Certified	Conception and evaluation of roadside testing instruments to formalise impairment evidence in drivers
CFF	Critical flicker fusion
CI	Confidence interval
CLT	Circular lights task
CRT	Choice reaction time
CTT	Critical tracking test
DG-TREN	Directorate-General for Energy and Transport
DRUID	Driving under the influence of drugs, alcohol and medicines
DSST	Digit symbol substitution test
DUID	Driving under the influence of drugs
EEG	Electroencephalogram
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
FTT	Finger tapping test
GHB	Gamma-hydroxybutyrate
HCl	Hydrogen chloride
ICADTS	The International Council on Alcohol, Drugs and Traffic Safety
Immortal	Impaired motorists, methods of roadside testing and assessment for licensing
LARS	Line analogue rating scale
LMT	Learning memory task
MAOI	Monoamine oxidase inhibitor

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 exam
MRT	Motor reaction time
NRI	Selective norepinephrine (noradrenaline)-reuptake inhibitor
OR	Odds ratio
PASAT	Paced auditory serial addition task
PIR-O	Proportional impairment ratios for objective evidence
RIMA	Reversible inhibitor of MAOI-A
Rosita	Roadside testing assessment
RR	Relative risk
RRT	Recognition reaction time
RVIPT	Rapid visual information processing task
SDLP	Standard deviation of lateral position
SFTA	'Société Française de Toxicologie Analytique': French Society of Analytical Toxicologists
SNRI	Serotonin/norepinephrine-reuptake inhibitor
SRT	Simple reaction time
SSRI	Selective serotonin-reuptake inhibitor
TCA	Tricyclic antidepressants
THC	$\Delta^9$ -tetrahydrocannabinol
THC-COOH	11-nor- $\Delta^9$ -THC-9-carboxylic acid
TIAFT	The International Association of Forensic Toxicologists
TMT	Trail making test
TRT	Total reaction time
WAIS	Wechsler adult intelligence scale
WCST	Wisconsin card sorting task

# Appendix

Table A1: Results of roadside surveys							
	Australia P. Swann (pers. com.) (1)	Canada Dussault et al. (2002)	Denmark Behrensdoerff and Steenstoff (2003)	Netherlands Mathijssen (1999) (2)	Norway Assum et al. (2005)	United Kingdom Assum et al. (2005) (3)	United States Lacey et al. (2007) (4)
Year	2004–2005	1999–2000	2000	1997–1998	2003–2004	2003–2004	2005
Sample size	4 200	11 574 (A) 5 931 (D)	896	893	410	1 312	639
Sample	Breath (A), saliva (D)	Breath (A), urine (D)	Saliva	Urine	Blood or urine	Oral fluid	Oral fluid and/ or blood
Weighted	No	Yes	No	No	Yes	Yes	
Alcohol		5.1 %		>0.2% <sup>o</sup> : 10.2 % >0.5% <sup>o</sup> : 4.9 %	>0.2% <sup>o</sup> : 2.1 %		
Drugs (illicit)	0.9% (5)	11.8 %	1.9% (1.3%)	6.4%	9.9%	10.8 %	15.0%
Drugs and alcohol		0.7 %		>0.2% <sup>o</sup> : 1.3 % >0.5% <sup>o</sup> : 0.8 %	>0.2% <sup>o</sup> : 0.3 %		
Amphetamine		0.1 %	0.1 %	0.5% (6)	0.03 %	0.7 %	2.2% (7)
Methamphetamine	0.7%			(8)			
MDMA				0.1 %	0.6 %	4.6% (9)	
Cocaine		1.1 %	0.1 %	0.7 %	0.7 %	1.3 %	2.2 %
Cannabis	0.3 %	6.7 %	0.7 %	4.6 %	4.5 % (10)	3.3 %	7.4 %
Benzodiazepines		3.6 %	0.6 %	0.6 %	2.1 %	0.2% (10)	1.6 %
Opiates		1.2 %	0.3 %	0.5% (C) 0.1 % (H)	0.1 % (M/H) 0.6 % (C)	0.2% (10) 1.6% (C)	1.1 %
Methadone					0.04 %		0.2 %
Barbiturates		0.5 %					0.3 %
TCA					0.3 %		0.2 %
PCP		0.03 %					

(1) Negative for alcohol. (2) Only during weekend nights. (3) Glasgow. (4) Pilot test study; only during weekend nights. (5) Only tested for the presence of cannabis and methamphetamine. (7) Also pseudoephedrine, phentermine and phenylpropranolamine. (8) See amphetamine. (9) MDMA/MDA/MDEA. (10) Only this substance present; no combinations.

Abbreviations: A, alcohol; D, drugs; C, codeine; H, heroin; M, morphine.





**Table A3: Prevalence of drugs, medicines and/or alcohol in drivers killed in traffic accidents**

	Australia Drummer et al. (2005)	Canada Brault et al. (2004)	France Mura et al. (2006)	Hong Kong Cheng et al. (2005)	Italy Sironi et al. (1999)	Vignali et al. (2001)
Year	1990-1999	1999-2002	2003-2004	1996-2000	1986-1996	1987-1999
Sample size	3 398	855	2 003	197	129	119
Sample	Blood	Blood and urine	Blood	Blood (A), blood and urine (D)	Blood (A), blood and urine (D)	Blood
Remarks			< 30 years		1 vehicle crash	Deceased within 4 hours
Alcohol	>0.5% <sup>acc.</sup> : 29.1%	33.5% >0.8% <sup>acc.</sup> : 28.5%		>0.5% <sup>acc.</sup> : 24.9%	55.8% >0.1% <sup>acc.</sup> : 48.1%	47.9%
Drugs	26.7%	24.7%		6.1%		21.9%
Drugs and alcohol	9.7%	11.7%		2.5% >0.5% <sup>acc.</sup> : 2.0%		16.0%
Amphetamine	4.1% (1)	0.4%	3.1%			0.0%
Methamphetamine	(2)			1.5%		
MDA	(2)				0.8%	
MDMA	(2)			1.5%		0.0%
Cocaine	(2)	4.7%	3.0%		4.7%	8.4%
Cannabis	13.5%	13.1%	28.9%	2.0%	4.7%	8.4%
Benzodiazepines	4.1%	9.2%		1.0%	3.9%	5.9%
Opiates	4.9% (3)	1.3%	1.9% (M)			3.4%
Methadone					3.9%	0.8%
Barbiturates		0.4%			2.3%	1.7%
Phencyclidine		0.5%				
Ephedrine				1.0%		
Ketamine				0.5%		
Propylphenazone				0.5%		
Others					3.1%	

Table A3 continued

	Spain		Sweden		United Kingdom		United States	
	del Rio et al. (2002)	Lopez-Rivadulla and Cruz (2000)	Holmgren et al. (2005)		Assum et al. (2005)		Logan and Schwilke (2004), Logan (2005)	
Year	1991-2000	1996-1998	2000-2002		1998-2002		2001-2002	
Sample size	5 745	33	855		22		370	
Sample	Blood	Blood and urine	Blood and urine		Blood		Blood and serum	
Remarks					Glasgow			
Alcohol	43.8% >0.8% <sup>oc</sup> ; 32.0%	58.9%	>0.2% <sup>oc</sup> ; 22.2%		36.36%		>0.1% <sup>oc</sup> ; 44.0%	
Drugs		10.0% (4)			13.6%		35.0%	
illicit	8.8%		8.1%					
medicinal	4.7%		19.4%					
Drugs and alcohol	5.6%	7.0%	>0.2% <sup>oc</sup> ; 4.9%		4.6% (5)		17.0%	
Amphetamine	1.2%		5.2%		(6)		4.9%	
Methamphetamine			0.8%		(6)			
MDMA	0.6%		0.9%				3.5%	
Cocaine	5.2%		0.5%				12.7%	
Cannabis	2.2%		3.9%				4.1%	
Benzodiazepines	3.4%		7.6%		Diazepam: 4.6%		1.6% (M)	
Opiates	3.2%				4.6% (M)		1.9% (HC)	
Methadone			0.1%					
Barbiturates	0.3%							
Antidepressants	0.6%							
Phenyljoin								
Painkillers	0.5%							
Others			0.6%				1.9%	

(1) Includes, methamphetamine, MDMA, cocaine, (pseudo)ephedrine and phentermine. (2) See amphetamine. (3) Morphine, 6-acetylmorphine, codeine, methadone, propoxyphene and meperidine. The presence of heroin was confirmed by means of 6-acetylmorphine. (4) Only this substance, no combinations. (5) Including methamphetamine and MDMA. (6) See amphetamine.

Abbreviations: A, alcohol; D, drugs; HC, hydrocodon; M, morphine.

**Table A4: Prevalence of drugs, medicines and/or alcohol in drivers involved in a traffic accident**

	France			Greece
	Pépin et al. (1999)	Pépin et al. (2003)	Laumon et al. (2005)	Maravelias (2003)
Year	1999	2001	2001-2003	1995-2002
Sample size	164	3 751	10 748	2 712
Sample	Blood	Blood	Blood	Blood (A), urine (D)
Remarks	Severe or fatal accident	Fatal accident	Fatal accident	
Alcohol >0.5‰				37.2%
Drugs		17.0% (1)	7.9%	5.1% (2)
Drugs and alcohol >0.5‰	19.5%			4.2%
Amphetamine	0.6%	1.7%	0.5%	1.0% (3)
Cocaine	0.0%	0.8%	0.2%	
Cannabis	15.9%	13.7%	7.0%	4.0%
Benzodiazepines				4.0%
Opiates	3.1%	3.5%	0.9%	3.7%

(1) Only one drug present, no combinations with another drug or alcohol.

(2) Only drugs present, no combinations with alcohol.

(3) Also includes cocaine.

Abbreviations: A, alcohol; D, drugs.

Table A5: Prevalence of drugs in drivers suspected of driving under the influence of drugs

	Australia Koslos et al. (2003) (1)	Belgium Maes et al. (2003) (2)	Raes and Verstraete (2005)	Finland Lillsunde (2000)	France Pépin et al. (1999) (3)	Germany Toennes et al. (2005) (4)	Iceland Thorsdottir et al. (2004)	Luxembourg Wenig (2005) (5)
Year	2000–2003	2000–2001	2000–2005	1998	1998	2001	2000–2002	1999–2002
Sample size	311	896 (D) 128 (M) 123 (A)	450	1 323	94	168 (A) 131 (D)	162	481
Sample	Blood	Plasma	Plasma	Blood	Blood	Blood (A), serum (D)	Blood and/or urine	Blood
Alcohol		37.0% >0.5‰: 26.0%				>0.5‰: 13.1%	11.7%	39.1%
Drugs								
illicit	99.0%			84.0%	56.4%		56.1%	
Amphetamine	21.0%	85.2%	19.9%	57.0%	4.3%	27.5%	24.7%	3.1%
MDMA		54.2%	20.4%					
Cocaine	0.3%	18.7%	17.9%		2.1%	16.0%	2.5%	10.8%
Cannabis	29.0%	54.6%	73.5%		34.0%	80.9%	38.9%	39.9%
Benzodiazepines	63.0%	11.7%		64.0%			43.2%	26.2%
Opiates	38.0%	1.4%	2.7%		16.0%	19.1%	16.0%	
6-acetylmorphine (6)								21.6%
Methadone		3.9%						14.1%
Antidepressants		3.9%					5.6%	
Neuroleptics							3.7%	
Others							9.9%	

	Netherlands		Norway		Slovenia		Sweden		Switzerland	
	Smink et al. (2001)	Christoffersen (2000)	Zorec-Karlovsek et al. (2003)	Ceder (2000)	Jones (2005) (7)	Plaut and Staub (2000)	Augsburger et al. (2005)			
Year	1995-1998	1998	1994-2001	1999	2002	1995-1999	2002-2003			
Sample size	1 665	4 417	3 602	Unknown	5 051	311	440			
Sample	Blood or urine	Blood	Blood or urine	Blood	Blood	Urine	Blood			
Alcohol		66.8%	55.0%	91.0%		>0.1% <sup>(a)</sup> : 60.5%	46.1%			
Drugs		29.3%	5.1%	43%, 63% <sup>(b)</sup>	59.0%	8.4%	89.1%			
Amphetamine	14.4%			1.0%			3.6%			
MDMA	5.2%			2.0%	4.9%		6.4%			
Methamphetamine	32.7%		4.4%	1.0%	3.0%	19.6%	12.5%			
Cocaine	21.8%	31.4%	35.7%	21%, 30% <sup>(b)</sup>	29.0%	53.7%	59.3%			
Cannabis	32.6%		8.2%			31.2%	13.0%			
Benzodiazepines		20.3%		23%, 17% <sup>(b)</sup>	14.6%		2.3%			
diazepam		11.9%		19%, 7% <sup>(b)</sup>	14.6%		5.5% (De), 4.8% (Mi),			
flunitrazepam					2.3% (Ni)		2.3% (Ox), 1.4% (Lo)			
others							9.1%, 4.8% (C)			
Opiates	18.8%		15.1%	12%, 10% <sup>(e)</sup>	6.3% (C)	27.0%	7.3%			
morphine		10.7%			9.0%					
6-acetylmorphine <sup>(4)</sup>		7.2%			2.4%					
Methadone	10.4%		12.8%	14.4%		21.5%	7.1%			
Barbiturates	0.9%		1.0%	1.0%		5.5%				
GHB				2.0%						
TCA	1.6%									
Zolpidem							1.1%			
Others	14.5%		3.4%				< 2%			

(1) Positive field sobriety test. (2) Positive field sobriety test and urine test. M/A: only tested in false positives for drugs. (3) Involved in a severe or fatal accident. (4) Scandal. (5) Involved in a traffic accident. (6) To determine heroin use. (7) Jones (2005) describes data for 2000, 2001 and 2002, only the data for 2002 are given in the table, but data for 2000 and 2001 were similar. (8) First value is before implementation of new legislation, second is after implementation. Abbreviations: A, alcohol; C, codeine; D, drugs; M, medicines; Ni, nitrazepam; De, desmethyldiazepam, Mi, midazolam, Ox, oxazepam; Lo, lorazepam.

**Table A6: Prevalence of drugs and/or medicines in drivers suspected of driving under the influence of alcohol**

	Germany		United Kingdom
	Rentsch et al. (2002)	Römhild et al. (2005)	Officer (2003)
Year	2000-2001	2002	1996-2000
Sample size	673	1 199	102
Sample	Serum	Serum	Biological samples
Remarks	Young drivers involved in a traffic accident	Hannover, Göttingen, Magdeburg, Halle and Leipzig	Scotland
Drugs		7.8%	33.0%
Combination of drugs			8.8%
Amphetamine	10.2%	1.3%	
Cannabis	23.0%	5.3%	25.0% (1)
Benzodiazepines		1.7%	(2)
Cocaine	4.6%	0.0%	
Opiates - morphine		0.2%	

(1) Also includes benzodiazepines.

(2) See cannabis.

**Table A7: Results of recent surveys that report data of the general (driving) population**

Country (study)	Year	Target group	N	Results
Australia (Australian Institute of Health and Welfare, 2001)	2001	General population	27 000	Has driven a vehicle during the previous 12 months under the influence of drugs: 3.9%
Australia (Australian Institute of Health and Welfare, 2004)	2004	General population	30 000	Has driven a vehicle during the previous 12 months under the influence of drugs: 3.3%
Canada (Ontario) (Walsh and Mann, 1999)	1996–1997	Drivers	4 735	Has driven a vehicle during the previous 12 months under the influence of cannabis: 1.9%
Canada (Ontario) (Adlaf et al., 2003b)	2002	Drivers	2 129	Has driven a vehicle during the previous 12 months under the influence of cannabis: 2.9%
Canada (Beirmess et al., 2003)	2002	Drivers (survey by telephone)	1 214	Has driven a vehicle during the previous 12 months within 2 hours after the use of: – a drug: 17.7% – a prescribed medicine: 2.2% – cannabis: 1.5% – other illicit drug: 0.9%
Denmark (Behrendtsch and Steentoft, 2003)	2000	Drivers (Roadside survey)	636	– taken psychoactive medicine or drugs within 24 hours before being stopped: 3% – used cannabis within 24 hours before being stopped: 0.2% – ever driven a vehicle under the influence of an illicit drug: 2.8% – ever driven a vehicle a few hours after the use of an illicit drug and alcohol: 4% – ever driven a vehicle a few hours after the use of a psychoactive medicine and alcohol: 8.5%
			376	– ever driven a vehicle under the influence of alcohol above the legal limit (0.5‰): 24.5%
Spain (del Rio and Alvarez, 2001)	1999	Drivers (survey in medical driving test centres)	8 043	Problems with illicit drugs (abuse, dependent): 0.3% (of whom, 62.5% drive a vehicle daily; 12.5% 1 to 2 times a week; 8.3% occasionally) and 16.7% have not driven a vehicle during the last year
United Kingdom – Scotland (Neale et al., 2000)	2000	Drivers (survey at toll bridges) 17–39 years	273	Problems with illicit drugs and with alcohol: 0.15% Ever driven a vehicle within 12 hours (not for alcohol) after the use of: – cannabis: 1.5% – alcohol: 64% – ecstasy: 4% – cocaine (crack): 3% (1%) – LSD/heroin: 1%
		Drivers (survey at toll bridges) >40 years	264	Ever driven a vehicle within 12 hours (not for alcohol) after the use of: – cannabis: 3% – alcohol: 65% – ecstasy: 0% – cocaine (crack): 1% (0%) – LSD/heroin: 0%
United States (SAMHSA, 2006)	2004	General population (estimation for 240 million)		Driven a vehicle during previous 12 months under the influence of: – illicit drugs: 4.4% – alcohol: 13.5%
	2005	General population (estimation for 244 million)		Driven a vehicle during previous 12 months under the influence of: – illicit drugs: 4.3% – alcohol: 13%



Table A8: Results of recent surveys that report data of young drivers

Country (study)	Year	Target group	N	Results
Australia (Lenton et al., 1999)	1995	Persons attending a rave (Perth) during the past 6 months	66	On the way to the rave, the driver was: <ul style="list-style-type: none"> <li>- completely sober: 45%</li> <li>- 'ok', but he has used drugs: 30%</li> <li>- under the influence of drugs: 12%</li> </ul> On the way home from the rave, the driver: <ul style="list-style-type: none"> <li>- had not used drugs: 13% (driver was family member or bus driver)</li> <li>- had used drugs a while ago, but was no longer under the influence: 57%</li> <li>- under the influence of drugs or very tired (fell asleep driving): 30%</li> </ul>
Australia (Lenné et al., 2004)	2002	Drivers 18-24 years	1 184	Driven a vehicle under the influence of recreational drugs: 15%
Australia (Davey et al., 2005)	2005	University students	275	Driving under the influence of: <ul style="list-style-type: none"> <li>- drugs: 25%</li> <li>- alcohol: 14%</li> <li>- alcohol and drugs: 8%</li> </ul>
Canada (Ontario) (Adlaf et al., 2003a)	2001	Students with a driving licence	1 846	In the previous 12 months, has driven a vehicle within one hour after the use of: <ul style="list-style-type: none"> <li>- 2 or more alcoholic units: 15.1%</li> <li>- cannabis: 19.7%</li> </ul>
Canada (Asbridge et al., 2005)	2002-2003	Students (approx. 50% had a driving licence)	6 087	In the previous 12 months, has driven a vehicle under the influence of: <ul style="list-style-type: none"> <li>- cannabis: 15.1%</li> <li>- alcohol: 11.7%</li> </ul>
United Kingdom - Scotland (Neale et al., 2000)	2000	Visitors of dance or night clubs that have a driving licence	58	Ever driven a vehicle within 12 hours (not for alcohol) after the use of: <ul style="list-style-type: none"> <li>- cannabis: 59%</li> <li>- alcohol: 69%</li> <li>- crack: 5%</li> <li>- ecstasy: 3.6%</li> <li>- LSD/heroine: 3%</li> <li>- amphetamines: 2.8%</li> </ul>
United Kingdom (Terry and Wright, 2005)	2005	University students (87% are drivers)	46	Ever driven a vehicle under the influence of: <ul style="list-style-type: none"> <li>- cannabis: 40%</li> <li>- alcohol: 7.5%</li> </ul> Tries to neutralise the effects of cannabis and/or alcohol before driving by drinking coffee, or by eating: 12.9%
United States (SAMHSA, 2006)	2004	Persons aged 18-25 years (estimation for 32 million)		In the previous 12 months, has driven a vehicle under the influence of: <ul style="list-style-type: none"> <li>- illicit drugs: 13.3%</li> <li>- alcohol: 25%</li> </ul>
	2005	Persons aged 18-25 years (estimation for 32 million)		In the previous 12 months, has driven a vehicle under the influence of: <ul style="list-style-type: none"> <li>- illicit drugs: 13.4%</li> <li>- alcohol: 25%</li> </ul>

**Table A9: Results of recent surveys that report the data of drug users**

Country (study)	Year	Target group	N	Results
Australia (Victoria) (Aitken et al., 2000)	2000	Injecting drug users (heroin and/or amphetamine)	160	<p>Does not have a driving licence: 9.5%</p> <p>Has driven a vehicle last week:</p> <ul style="list-style-type: none"> <li>- directly after injecting: 67.1%</li> <li>- during initial withdrawal symptoms: 20%</li> <li>- 'stoned': 22.8%</li> <li>- opiate-induced drowsiness: 22.8%</li> <li>- fallen asleep behind the wheel: 2.5%</li> </ul> <p>Circumstances of last car accident:</p> <ul style="list-style-type: none"> <li>- recently injected drugs: 31.4%</li> <li>- initial withdrawal symptoms: 13.7%</li> <li>- 'stoned': 37.3%</li> <li>- under the influence of a high dose of alcohol: 9.8%</li> </ul>
Australia (Lenné et al., 2001)	2001	Young cannabis users with driver's licence	67	<p>43% of the times they use cannabis, they drive a vehicle</p> <p>14% of the times they use alcohol and cannabis, they drive a car</p>
Australia (Sydney) (Darke et al., 2004)	2002	Injecting drug users (ever driven a vehicle)	286	<p>Ever driven a vehicle shortly after the use of:</p> <ul style="list-style-type: none"> <li>- cannabis: 74%</li> <li>- heroin: 71%</li> <li>- amphetamine: 53%</li> <li>- alcohol (three alcoholic units): 51%</li> </ul> <p>While driving under the influence of drugs:</p> <ul style="list-style-type: none"> <li>- ever been involved in a traffic accident: 32%</li> <li>- ever been injured in traffic accident: 15%</li> <li>- ever injured other persons in a traffic accident: 8%</li> <li>- ever someone hospitalised in a traffic accident: 12%</li> <li>- ever someone killed in a traffic accident: 1%</li> </ul> <p>In the previous 12 months, driven a vehicle shortly after the use of:</p> <ul style="list-style-type: none"> <li>- cannabis: 57%</li> <li>- heroin: 56%</li> <li>- amphetamines: 34%</li> <li>- alcohol (three alcoholic units): 27%</li> </ul> <p>In the previous 12 months, been involved in a traffic accident while under the influence of drugs: 9%</p>

Australia – Sydney/Newcastle (Jones et al., 2005)	2004–2005	Current cannabis users	320	In the previous 12 months, has driven a vehicle within one hour after the use of: – cannabis alone: 78 % – cannabis and other drug: 30 %
Canada (Ontario) (Walsh and Mann, 1999)	1996–1997	Cannabis users with a driving licence	368	In the previous 12 months, has driven a vehicle after the use of cannabis: 23 %
Germany (Kubitzki, 2001)	2001	Young drug users (survey in night clubs, discos)	225	Regularly drives a vehicle under the influence of: – drugs: 94 % – ecstasy: 83 % – cannabis: 67 % Confirms driving under the influence of drugs and alcohol: 92 % Ever involved in a traffic accident while under the influence of drugs: 14 %
United Kingdom (Albery et al., 2000)	2000	Drug users that drove a car in the previous 12 months	71	Driven a car in the last year (last month) directly after the use of: – alcohol: 85.9 % (78.9 %) – illicit drugs: 81.7 % (–) – cannabis: 80.3 % (76.1 %) – heroin: 59.2 % (57.7 %) – stimulants: 50 % (29.6 %) – methadone: 49.3 % (42.3 %) Been involved in at least one car accident: – as driver: 41.4 % – as driver shortly after drug use: 21.1 %
United Kingdom – Scotland (Neale et al., 2000)	2000	Drivers who use drugs recreationally (survey by telephone)	61	Ever driven a vehicle shortly after the use of: – an illicit drug: 85.2 % – cannabis: 72.1 % – alcohol (above legal limit): 41 % – ecstasy: 42.6 % – amphetamine: 24.6 % – cocaine: 11.5 % – LSD: 8.2 %
United Kingdom (Terry and Wright, 2005)	2005	Regular cannabis users (96.8 % are drivers)	63	Ever driven a vehicle under the influence of: – cannabis: 82 % – alcohol (more than 4 units): 23 % Tries to neutralise the effects of cannabis and/or alcohol by drinking coffee, or by eating: 27.6 %
United States (Buchan et al., 2000)	1998	Adult cannabis users with a driving licence	82	Driven a vehicle during the past year while under the influence of alcohol or illicit drugs: 22 %
			101	Ever been arrested for driving under the influence: 3 %

**Table A10: Results of experimental studies on benzodiazepines**

Substance	Study	Tests	Doses	Effect
Zaleplon (Za) Zolpidem (Z)	Danjou et al. (1999)	CRT, DSST, CFF	Za = 10 mg Z = 10 mg	Z effects visible next morning
Zaleplon Zolpidem Triazolam (Tr)	Troy et al. (2000)	Memory Learning	Za = 10 or 20 mg Z = 10 or 20 mg Tr = 0.25 mg	Cognitive impairment with Z and Tr after 8.25 hours after administration
Zolpidem Zaleplon	Hindmarch et al. (2001b)	CFF CRT DSST	Z = 10 mg Za = 10 or 20 mg	Z had more residual effects than Za 20 mg
Zolpidem Zaleplon	Verster et al. (2002b)	Memory Psychomotor performance	Z = 10 or 20 mg Za = 10 or 20 mg	Z affected performance in dose-dependent manner
Zaleplon Zolpidem	Stillwell (2003) Logan and Couper (2001)	Driving cases		Driving impairment
Triazolam Amphetamine	Mintzer and Griffiths (2007)	Memory tasks	Tr = 0.25 or 0.5 mg/70 kg D = 20 or 30 mg/70 kg	Amphetamine did not reverse effects of triazolam
Zaleplon review	Patat et al. (2001)		Za = 10 or 20 mg	No effect with zaleplon 10 mg
Triazolam Zolpidem	Mintzer and Griffiths (1999)	Memory	Tr = 0.125, 0.25 or 0.5 mg/70 kg Z = 5, 10 or 20 mg/70 kg	Impairment for triazolam
Triazolam	Greenblatt et al. (2005)	DSST-EEG correlation	Tr = 0.375 mg	High degree of correlation
Zaleplon Zopiclone (Zo) Alcohol	Vermeeren et al. (2002b)	Highway driving test	Za = 10 mg Zo = 7.5 mg BAC = 0.3 g/l	No impairment for zaleplon
Alprazolam (A) Dextroamphetamine (Dex)	Mills et al. (2001)		A = 0.5 mg Dex = 10 mg	A impaired performance, Dex enhanced except with fatigue
Alprazolam	Verster et al. (2002a)	SDLP	A = 1 mg	Serious driving impairment
Alprazolam	Verster and Volkerts (2004b)	Memory		Dose-dependent impairment
Alprazolam XR	Leufkens et al. (2007)	Standardised driving test Memory Psychomotor tests	A = 1 mg	Severe driving impairment

Table A10 continued

Substance	Study	Tests	Doses	Effect
Alprazolam	Bentué-Ferrer et al. (2001)	Behaviour	A = 0.005 mg/kg	Stimulatory effect
Alprazolam	Snyder et al. (2005)	Attention Psychomotor function	A = 0.5 or 1 mg	0.5 mg reduced attention, 1 mg reduced psychomotor performance and attention
Lorazepam (Lor) Ritanserin (Ri)	Van Laar et al. (2001)	SDLP	Lor = 1.5 mg <i>bid</i> Ri = 5 mg	Lor showed marked driving impairment
Lorazepam	Matthews et al. (2002)	Memory	Lor = 2.5 mg	Impairment to learn behavioural strategies
Lorazepam	Izaute and Bacon (2006)	Memory	Lor = 0.038 mg/kg	Impairment
Lorazepam	Clarkson et al. (2004)	Driving cases		Driving impairment
Lorazepam Alcohol	Soo-ampon et al. (2004)	Recall memory	Lor = 2 mg BAC = 0.6 g/l	Impairment for both substances
Lormetazepam (Lorm)	Judice et al. (2002)	Daytime vigilance Driving simulation	Lorm = 1 mg	No effect next morning
Lormetazepam	Fabbrini et al. (2005)	SRT CRT		Lorm had no effect
Temazepam (Te) Alcohol	Tiplady et al. (2003)		Te = 20 or 30 mg BAC = 0.8–1.0 g/l	Te slowed performance, alcohol generated more errors
Temazepam	Morin et al. (2003)		Te = 7.5 or 30 mg	Few effects and tolerance
Flunitrazepam (Flu) Clonazepam (Cl)	Dowd et al. (2002)	Behaviour and cognitive	Flu = 2 mg Cl = 3 mg	Flu had an effect up to 4 hours after intake, Cl for 6 hours
Flunitrazepam	Bramness et al. (2006)	Blood level-impairment degree correlation		Clear correlation
Diazepam	Rich et al. (2006)	Memory	Di = 0.19 mg/kg	Impairment
Zolpidem Zopiclone Flunitrazepam	Bocca et al. (1999)		Z = 10 mg Zo = 7.5 mg Flu = 1 mg	Residual effects in morning for Zo en Flu
Lorazepam Flurazepam Nitrazepam Temazepam	Vignola et al. (2000)	Memory Attention Psychomotor function		Unmedicated insomniacs performed worse than medicated ones

**Table A10 continued**

Substance	Study	Tests	Doses	Effect
Temazepam Triazolam Alcohol	Simpson and Rush (2002)		Te = 15 or 30 mg Tr = 0.125 or 0.25 mg BAC = 0.5 g/l	Te and Tr alone had some impairment, combined with alcohol = worse
Zolpidem Temazepam	Partinen et al. (2003)		Z = 10 mg Te = 20 mg	No difference between drugs and placebo
Zolpidem Zopiclone Lormetazepam	Allain et al. (2003)	LMT CTT SRT Sternberg test	Z = 5 mg Zo = 3.75 mg Lorm = 1 mg	Lorm gave impairment LMT
11 benzodiazepines	Vermeeren (2004)		Za = 10 or 20 mg Te = 20 mg Lor = 1 mg Tr = 0.125 mg	4 benzodiazepines were unlikely to have residual effects
Temazepam Diphenhydramine (Di) Valerian (Val)	Glass et al. (2003)	DSST Manual tracking	Te = 15 or 30 mg Dip = 50 or 75 mg Val = 400 or 800 mg	No impairment with Val and Di 50 mg
Zolpidem Zopiclone Lormetazepam	Staner et al. (2005)	Driving simulation EEG	Z = 10 mg Zo = 7.5 mg Lorm = 1 mg	Zolpidem had no effect
Zopiclone Zolpidem Flunitrazepam	Berthelon et al. (2003)	Collision anticipation	Zo = 7.5 mg Z = 10 mg Flu = 1 mg	Flunitrazepam had a negative effect
Melatonin (Mel) Zaleplon Zopiclone Temazepam	Paul et al. (2003)	Serial reaction time Logical reasoning	Mel = 6 mg Za = 10 mg Zo = 7.5 mg Te = 15 mg	Melatonin shows no impairment
Dose-dependent driving impairment benzodiazepines	Bramness et al. (2002)	Apprehended drivers		Clear drug concentration effect

**Table A11: Results of experimental studies on antihistamines**

Substance	Author	Tests	Doses	Effect
Diphenhydramine	Richardson et al. (2002)		50 mg <i>bid</i>	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 <i>bid</i>	Less somnolence than 1st generation, not more than 2nd generation
Mequitazine	Theunissen et al. (2006b)	SDLP	5, 10, 15 mg	Dose-related increase
Chlorpheniramine	Mochizuki et al. (2002)	PET scan		
Chlorpheniramine	Serra-Grabulosa et al. (2001)	Auditory attention	4 mg	Impairment
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	Valck 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

**Table A11 continued**

Substance	Author	Tests	Doses	Effect
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-Cócerca et al. (2005)		10 mg	Somnolence
Cetirizine	Nordness and Zacharisen (2003)		50 mg	No
Cetirizine	Vermeeren et al. (2002a)	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. (2006a)		360 mg	No
Fexofenadine	Ridout et al. (2003b)		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, fexofenadine: no effect
Fexofenadine (F) versus cetirizine (C)	Tashiro et al. (2004)	CRT, SRT	F = 120 mg C = 20 mg	F less impairing than C
Bepotastine (B) versus cetirizine, fexofenadine and olopatadine (O)	Takahashi et al. (2004)	Sedation, psychomotor performance	B = 10 mg <i>bid</i> C = 10 mg F = 60 mg <i>bid</i> O = 5 mg <i>bid</i>	O most impairing and B least impairing
Levocetirizine versus desloratadine	Passalacqua and Canonica (2005)	Memory, attention, alertness		No
Cetirizine versus loratadine (Lo)	Salmun et al. (2000)		C = 10 mg Lo = 10 mg	Lo less somnolence



Table A11 continued

Substance	Author	Tests	Doses	Effect
Inter-drug differences	Shamsi and Hindmarch (2000)			Fexofenadine and ebastine least effect
Prescription-event monitoring	Mann et al. (2000)			Fexofenadine and loratadine least effect
Letter	Ramaekers and Vermeeren (2000)			Fexofenadine, ebastine and loratadine no effect
Desloratadine and levocetirizine	Layton et al. (2006)			Less sedation with desloratadine
Review	Meltzer (2005)			Fexofenadine, loratadine, and desloratadine no effect
Fexofenadine versus hydroxyzine	Tashiro et al. (2005)	BRT	F = 120 mg H = 30 mg	F 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	F = 120 mg O = 10 mg	F no effect
Ebastine (E) versus chlorpheniramine	Tagawa et al. (2002)	Cognitive impairment	E = 10 mg	E no effect
Loratadine versus diphenhydramine (Di)	Kay (2000); Kay and Quig (2001)	Divided attention	Lo = 10 mg Di = 50 mg	L no effect
Desloratadine (D) versus diphenhydramine	Wilken et al. (2003)		D = 5 mg Di = 50 mg	D no effect
Potential of alcohol	Barbanoj et al. (2006)			Hydroxyzine 30 mg > cetirizine 10 mg = olopatadine 20 mg > olopatadine 10 mg (non)
Tolerance to cetirizine, mequitazine, and dexchlorpheniramine	Theunissen et al. (2006b)	Driving impairment	M = 10 mg C = 10 mg Cl = 6 mg	Tolerance after 8 days
Levocetirizine (L) versus diphenhydramine	Verster et al. (2003b)	Memory, attention, tracking, SDLP	L = 5 mg Di = 50 mg	L no effect
Desloratadine versus diphenhydramine	Vuurman et al. (2004)	SDLP	D = 5 mg Di = 50 mg	D 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)		F = 60 mg Di = 50 mg	Di greater effect than alcohol

**Table A11 continued**

Substance	Author	Tests	Doses	Effect
Review	Verster and Volkerts (2004a)			F and L no effect
Levocetirizine versus cetirizine, loratadine, promethazine (P)	Hindmarch et al. (2001a)	CFF, CRT, continuous tracking task	L = 5 mg C = 10 mg Lo = 10 mg P = 30 mg	L no effect
Review	Moskowitz and Wilkinson (2004)			Effect depends on substance, generation, individual

Abbreviation: *bid, bis in die* (twice daily).

**Table A12: Results of experimental studies on performance effects associated with use of antidepressants**

Substance	Study	Tests	Doses	Effect
TCA (general)	Podewils and Lyketsos (2002)	MMSE		No
Amitriptyline	Veldhuijzen et al. (2006a)	SDLP	25 mg	Acute: impairment Chronic: tolerance
SSRI (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	No
Escitalopram	Rose et al. (2006)		10 mg	No
SSRI (general)	Wadsworth et al. (2005)			Impairment
Sertraline Paroxetine	Schmitt et al. (2002)	Vigilance Stroop	50–100 mg 40–60 mg	No
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	No
Citalopram	Harmer et al. (2002)	memory	10 mg IV	Positive effect
Fluoxetine (Fl) versus paroxetine (Pa)	Cassano et al. (2002)	Cognitive function	Fl = 10–40 mg Pa = 20–60 mg	No
Paroxetine	Hindmarch et al. (2000a)	Withdrawal		Impairment
Venlafaxine	O'Hanlon et al. (1998)	CFF, CTT, divided attention, Macworth	37.5–75 mg	No
Venlafaxine	Campagne (2005)	Withdrawal		Impairment
Milnacipran	Hindmarch et al. (2000b)	CFF	50+25 mg	No (young) Positive effect (old)
Milnacipran	Poirier et al. (2004)	CFF	50 mg <i>bid</i>	No
Milnacipran	Richet et al. (2004)		50 mg <i>bid</i>	No effect and no potentiation of alcohol

**Table A12 continued**

Substance	Study	Tests	Doses	Effect
Fluoxetine versus reboxetine (R)	Gallassi et al. (2006)		Fl = 10-40 mg R = 4-8 mg	Improvement
SSRI versus SNRI	Wingen et al. (2006b)			Impairment
All Antidepressants (AD)	Ramaekers (2003a)	SDLP		Sedating AD = impairment Non-sedating AD = no effect SSRI, mirtazapine better than TCA, SNRI
All Antidepressants (AD)	Brunnauer et al. (2006)	Fitness to drive		Sedating AD = impairment Non-sedating AD = no effect SSRI, mirtazapine better than TCA, SNRI
Paroxetine versus mirtazapine (M)	Ridout et al. (2003a)	BRT, CFF, CRT	Pa = 20 mg M = 15-30 mg	No effect for paroxetine
Fluvoxamine versus imipramine	Koetsier et al. (2002)	CPT		Both improvement
Fluoxetine (Fl) versus desipramine (De)	Levkovitz et al. (2002)	Memory	Fl = 20 mg De = 125-200 mg	Improvement Fl greater than De
Fluvoxamine (Fluv) versus dothiepine (Do)	Wilson et al. (2000)	Sleep	Fluv = 100 mg Do = 100 mg	Fluv decreased Do increased
Reboxetine versus imipramine (I)	Katona et al. (1999)	Somnolence	R = 4-6 mg I = 50-100 mg	R no effect
TCA and SSRI	Peretti et al. (2000)	CFF threshold BRT		TCA decreased CFF, BRT impaired
Paroxetine versus nortryptiline	Nebes et al. (2003)	Cognitive function in elderly		No change
Sertraline (S), fluoxetine and nortryptiline (N)	Doraiswamy et al. (2003)	Cognitive function	S = 50 mg Fl = 20 mg N = 25 mg	Improvement
Venlafaxine (V), dothiepine	Trick et al. (2004)	Cognitive function: CFF	V = 37.5 mg <i>bid</i> Do = 25+75 mg	No disruptive effect
Paroxetine and nortryptiline	Butters et al. (2000)	Memory and executive function		Improvement
Escitalopram (Es) versus mirtazapine	Wingen et al. (2006a)	Delayed verbal memory score	Es = 10-20 mg M = 30-45 mg	Es no influence
Sertraline versus nortryptiline	Coffey et al. (2002)	Shopping list task, DSST, MMSE	S = 50-100 mg N = 25-100 mg	S more positive effect
Tianeptine (T) versus mianserin (Mi)	Ridout and Hindmarch (2001)	CRT, CFF, BRT	T = 12.5-37.5 mg Mi = 30 mg	T no effect

**Table A12 continued**

Substance	Study	Tests	Doses	Effect
Hypericum	Timoshanko et al. (2001)	DSST	900–1800 mg	Impairment
	Siepmann et al. (2002)		extr: 255–285 mg	No
Moclobemide	Siepmann et al. (2004)	CFF, CRT, memory	150 mg <i>bid</i>	No

Abbreviation: *bid*, *bis in die* (twice daily).



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