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Performance and Behavioral Effects of Illicit Drugs

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INTRODUCTION

Abuse of illicit drugs is a widespread problem in society. In the year 2004 over nineteen million Americans were current illicit drugs users, defined as having used an illicit drug at least once in the past month, representing almost 8 percent of the population above twelve years of age (Substance Abuse and Mental Health Services Administration 2005). The term illicit drugs refers to a variety of compounds such as marijuana, cocaine, amphetamines, heroin, and various hallucinogens, including PCP and LSD, which are generally obtained through illegal channels. In addition, drug abuse also includes the non-medical use of prescription drugs, such as tranquillizers and sedatives, medicinal stimulants and analgesics, as well as the abuse of psychoactive compounds found in common household or industrial products (e.g. inhalants). Alcohol and nicotine, although illegal for youths, are not considered illicit drugs.

Illicit drugs can impair behavior and mental performance in various ways. They may cause sedation or over-activation. They can blur or distort perception, compromise a clear judgment of situations, impair decision-making and responding. The behavioral toxicity of a drug can be ascertained through a variety of methods, ranging from subjectively reported experiences to various kinds of epidemiological surveys and controlled experimental studies. Adverse behavioral effects may even be predicted solely on the basis of a drug's pharmacological properties (Riedel et al. 1998). Each method has its advantages and limitations. The

assessment of drug-induced changes with laboratory tests of specific cognitive and psychomotor functions in a controlled and supervised setting may have limited predictive value for real-life complex behaviors, such as driving (Moran 1999). Conversely, with a methodologically sound experimental design, any observed effects can be attributed to a clear factor, notably the administered drug, thus establishing a direct causal link between performance and use of a drug at a certain dose. Causality is particularly difficult to ascertain in cross-sectional epidemiological studies comparing groups of drug abusers to normal controls, since the influence of factors other than drug use is unknown. For example, pre-existing differences in characteristics and life-style cannot be excluded as potential discriminating factors.

The combined picture emerging from various viewpoints and research lines can provide insight into a drug's potential behavioral toxicity. Unfortunately, for many drugs, and particularly for illicit drugs, the data on effects on mental performance and potential risk are incomplete. Existing data are limited to narrow dose ranges, selected research subjects (often young healthy volunteers) and specific behavioral outcome parameters. Although effects in other circumstances may be inferred based on existing information, the actual demonstration of such behavioral effects, for example on driving capacity, remains essential.

This chapter provides an overview of the known behavioral and performance effects of the most commonly abused illicit drugs, with emphasis on driving ability. It will focus on the effects of acute drug intoxication, occurring at the time when the psychoactive substance is present in the body and exerting its pharmacological effects in the central nervous system (CNS). The long-term sequelae of drug abuse as behavioral changes that are the result of structural and irreversible brain damage from long-term exposure to neurotoxic compounds do not fall within the scope of this chapter. The cognitive, emotional and social effects of prolonged drug abuse are addressed in reviews, articles and book sections on various illicit drugs, e.g. cocaine (Nnadi et al. 2005; Verdejo Garcia et al. 2004), ecstacy (Gouzoulis Mayfrank and Daumann 2006; Montoya et al. 2002; Verdejo Garcia et al. 2004), amphetamines (McCann and Ricaurte 2004; Ornstein et al. 2000; Simon et al. 2000), marijuana (Ameri 1999; Hall 2006; Lundqvist 2005; Verdejo Garcia et al. 2004), inhalants (Cairney et al. 2002; Rosenberg et al. 2002; Uzun and Kendirli 2005), hallucinogens (Doering Silveira et al. 2005; Halpern and Pope 1999; Jansen 2000) and opiates (Darke et al. 2000; Davis et al. 2002; Verdejo Garcia et al. 2004).

PSYCHOSTIMULANTS

Psychostimulants boost the users' confidence and temporally enhance feelings of well being and euphoria. The fatigue-counteracting capability of these drugs also make them very popular among truck drivers and others who perform demanding jobs (Crouch et al. 1993). The three most used psychostimulants are cocaine, amphetamines (including methamphetamine) and ecstasy. Cocaine was the first widely used psychostimulant. Amphetamines soon followed, and different amphetamine analogues became available, including methamphetamine and dextro-amphetamine. Amphetamines are often used as a substitute for cocaine. The effects are similar, but amphetamines are cheaper and more available, and their effects are longer lasting. Ecstasy is popular among people in the dance and club scene. Ecstasy can rely for its effect on several derivatives, including MDA and MDE, but the original psychoactive substance of the drug, MDMA, is still the most popular.

COCAINE

Cocaine raises levels of the neurotransmitters dopamine and norepinephrine by inhibiting their reuptake into presynaptic terminals and to a lesser degree by acting as direct agonists. The influence of cocaine on the dopamine system seems to play a prominent role in the drugs' psychostimulant properties (Feldman et al. 1997; Gawin 1991; Izenwasser 1998).

Cocaine increases pulse rate, body temperature, glucose availability, pupil size, vasoconstriction, alertness, motor activity and restlessness and it counteracts sleep (Rush et al. 1999; Stillman et al. 1993). The drug heightens energy levels and enhances consciousness, talkativeness, feelings of euphoria and self-confidence (Higgins and Katz 1998). The cocaine "high" often is followed by a fatigue rebound with a period of anxiety, depression and paranoia (Higgins and Katz 1998). After higher doses, tremors, convulsions and a severe loss of coordination can occur (Feldman et al. 1997). High doses also can produce sleeplessness, anxiety, paranoia, psychosis, hypervigilance, hyperreactivity, increased impulsivity, compulsive behaviour and increased aggression (Higgins and Katz 1998; Licata et al. 1993).

Cocaine administration under experimental conditions has produced contrasting findings. Some investigators reported improved reaction time, performance speed, impulse control, enhanced attention and information processing (Farre et al. 1993; Higgins et al. 1990; Higgins et al. 1993; Johnson et al. 1998) (Fillmore et al. 2005; Stillman et al. 1993). Others found no effect of a single dose of cocaine on information processing, learning, recognition memory, simple and choice reaction time, concentration, and central nervous system processing capacity (Farre et al. 1993; Foltin et al. 1993; Higgins et al. 1990; Johnson et al. 1999; Rush et al. 1999).

Combined use of cocaine and alcohol is very common among cocaine abusers (Grant and Harford 1990). When cocaine and alcohol have been administered together under experimental conditions, cocaine compensated for impaired task performance that was observed with alcohol alone, including reaction speed and information processing (Farre et al. 1993; Higgins et al. 1993).

The influence of cocaine on driving performance has not been studied. In traffic situations, however, increased self-confidence, impulsivity and aggression could result in overestimation of one's driving performance and higher risk acceptance. Another expected problem for adequate driving performance is the rebound of sleep during withdrawal. In this stage, cocaine abusers can experience extreme fatigue, lack of concentration and anxiety. This impairs focus of attention, and therefore would impair driving performance. A combination of cocaine and ethanol use has been frequently identified in fatally injured drivers (Marzuk et al. 1990). This finding suggests that the reduction of alcohol-induced sedation does not lead to safer driving performance.

AMPHETAMINE

Amphetamine acts to release newly synthesized dopamine and norepinephrine and inhibit their reuptake (King and Ellinwood 1997). Under experimental conditions, small doses of amphetamines (5-20 mg) have been shown to increase arousal and improve task performance in fatigued, as well as non-fatigued, subjects. The effects include increases in reaction speed, vigilance, accuracy in a spatial delay response task, verbal reasoning, coordination and cognitive processing speed (Fleming et al. 1995; Koelega 1993; Newhouse et al. 1989). Enhanced memory was observed after 10 mg *d*-amphetamine due to improved consolidation of new

material (Soetens et al. 1995). Data from other studies, however, show that amphetamines did not affect task performance, including information processing and mental set shifting (Pickworth et al. 1997). The amounts administered in experiments resemble therapeutic dosages (2.5-60 mg), but amphetamine abusers often take much higher doses (50-300 mg) and multiple doses (Logan 1996; Newhouse et al. 1989; Pickworth et al. 1997).

In one study, methamphetamine abusers had used their regular dose of the drug during the seventy-two hours prior to assessment (Simon et al. 2000). The exact time between drug consumption and assessment was not given, but only 55 percent of subjects reported using methamphetamine on the day of assessment. Therefore, many subjects possibly were in withdrawal while being tested. They had problems manipulating information and were less able to combine information in new ways. They also had difficulty focusing on the task at hand, because they lacked the capacity to ignore irrelevant information. These observed impairing effects may indicate either reduced processing resources or reduced processing rate (Simon et al. 2000).

Silber et al (2005) (Silber et al. 2005) assessed the acute effects of dexamphetamine on simulated driving performance of 24 volunteers in a double blind, placebo controlled, cross-over design. Mean dexamphetamine blood concentrations were 83 ng/ml and 98 ng/ml at 120 min and 170 min post drug, respectively. Results indicated a decrease in overall simulated driving ability following dexamphetamine administration during the day-time but not the night-time scenario tasks. Contributing to this performance reduction, "incorrect signalling", "failing to stop at a red traffic light" and "slow reaction times" were the behaviours most strongly affected by dexamphetamine

Methamphetamine abusers admitted to trauma centres were most likely to have been injured in traffic accidents, whereas cocaine abusers' primary causes for admission were injuries caused by violence, such as gunshot or stab wounds and assaults (Schermer and Wisner 1999). This does not necessarily indicate safer driving after cocaine, in comparison to methamphetamine. Instead, it may reflect a relatively higher rate of traffic participation after the use of methamphetamine as seems to be confirmed by field studies. Although only two percent of voluntarily tested truck drivers tested positive for methamphetamine, twelve percent refused participation. The actual number of questioned truck drivers who had used methamphetamine, therefore, may be higher (Lund et al. 1988). In another study, methamphetamine was found in seven percent

of fatally injured truck drivers (Crouch et al. 1993). Complex behavioral tasks, such as driving, require rapid processing of incoming information and correct decision making in regard to other traffic and traffic signaling. Thus, incorrect or slowed information processing can be expected to reduce traffic safety.

Other impairing effects of amphetamines during withdrawal include extreme exhaustion (amphetamine abusers can go without sleep for up to a week), loss of concentration, paranoia and anxiety (Logan 1996). Typical amphetamine-related driving behaviors, which lead to arrest, accidents, or fatal car crash, include drifting in and out of lane of travel, weaving, drifting of the road, speeding, high speed collisions and erratic driving (Logan 1996).

In conclusion, a therapeutic dose of amphetamine will generally not severely reduce task performance and traffic safety. High doses, however, can impair driving performance during the acute phase by inducing hallucinations, panicky behavior and increased risk taking. During withdrawal the reduced capacity to ignore irrelevant information, manipulate and combine information, together with extreme exhaustion and confusion, mediate misinterpretation of information, wrong decision making, reduced attention, risk taking and dangerous driving.

ECSTASY

± 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) is a phenethylamine, structurally related to amphetamine and mescaline (De Man 1994; Morgan 2000). MDMA is a monoaminergic agonist that releases and inhibits reuptake of serotonin (White et al. 1996) and to a lesser extent of dopamine (Colado et al. 2004).

In some studies, single doses of MDMA (range 0.9 – 1.9 mg/kg) were not found to impair task performance, including selective attention, visual search, planning or retrieval from semantic memory (Downing 1986; Vollenweider et al. 1998a). In a study with MDMA doses of 75 and 125 mg, esophoria (squinting) was observed after the higher dose but there was no effect on simple reaction time (Cami et al. 1999). Several experimental have studies reported that single doses of MDMA (75-100 mg) produce stimulant effects and may improve tracking performance in laboratory and on-the-road driving tasks, movement speed and impulse control (Kuypers and Ramaekers 2006; Lamers et al. 2003; Ramaekers and Kuypers 2006;

Ramaekers et al. 2006a). Yet, these same studies have also reported detrimental effects of MDMA on timing ability, brake reaction time and verbal and spatial memory function that may be of crucial importance in traffic. In addition impaired coordination, concentration difficulties and hallucinations have been observed in people while under the influence of MDMA (Downing 1986; Schifano 1995; Vollenweider et al. 1998a).

Any cognitive or psychomotor impairment can compromise driving performance. Therefore, any combination of the observed impairing effects of MDMA is likely to seriously impair driving performance. The drug's use has already been linked to sometimes fatal car crashes (Henry et al. 1992; Moeller and Hartung 1997; Mørland 2000; Schifano 1995). Furthermore, in real life, MDMA doses may be higher than those administered under experimental conditions, and it may be combined with sedative psychoactive substances such as marijuana and alcohol. Experimental studies on combined use of MDMA and alcohol have without exception indicated that the stimulant effects of MDMA do not mitigate the impairing effects produced by alcohol on actual and simulated driving performance, impulse control and psychomotor performance (Hernandez-Lopez et al. 2002) (Brookhuis et al. 2004; Kuypers et al. 2006; Ramaekers and Kuypers 2006). The lack of mitigating effects of MDMA on alcohol induced impairment on measures of impulsivity or risk tasking and actual driving may be of particular importance in terms of road safety issues since most of the MDMA-impaired driving cases that have been reported in the scientific literature consist of drivers who have taken multiple drugs and/or alcohol (Logan and Couper 2001). In conclusion, the driving skills of persons under the influence of MDMA may be seriously impaired as indicated by its detrimental effects on time estimation, break reaction time, perception and memory functions.

CANNABIS

Cannabis sativa contains more than 400 chemical compounds, of which about sixty are cannabinoids. The cannabinoid primarily responsible for the drugs' physiological and psychological effects is Δ^9-tetrahydrocannabinol (THC). When entering the systemic circulation, THC is rapidly distributed in fatty tissues, including the brain, and full elimination from the body can take several days to weeks. Consequently, THC metabolites can be present in urine for an extended period after the last drug intake. To date, two cannabinoid receptors, CB_1 and CB_2, have been identified. Cannabinoid receptors are involved in analgesia,

cognition, memory, motor activity, control of appetite and vomiting. THC is generally used for recreational purposes because of its psychotropic properties, but it is also indicated in the medical treatment of pain, inflammation, glaucoma and the nausea associated with cancer therapy (Voth and Schwartz 1997).

THC is rapidly absorbed during cannabis smoking and its peak effects appear after thirty to sixty minutes. Acute subjective effects are dose dependent, and their duration is two to four hours. Subjectively, the principal psychological effect of THC is euphoria or a "high". This state is sometimes accompanied by a mild state of anxiety, tension and confusion. Acute consumption of cannabis is associated with impairment of a variety of cognitive and psychomotor tasks, including memory, sense of time, motor coordination, and reaction speed. Memory impairment is the most consistently reported cognitive deficit. The acquisition or consolidation of newly learned information and work seems particularly impaired after an acute dose of THC (Ameri 1999; Robbe 1994).

Numerous experimental studies have investigated the effects of THC on isolated psychological functions and skills related to driving performance. These have generally shown that THC amounts between 40 and 300 µg/kg cause a dose dependent reduction in performance on laboratory tasks of attention, reaction time, tracking, or motor control (Robbe 1994). Results from driving simulator and closed-course studies of THC doses up to 250 µg/kg have generally failed to demonstrate severe effects (Attwood et al. 1981 ; Casswell 1977 ; Peck et al. 1986; Smiley et al. 1981; Stein et al. 1983). Results of these studies have shown differences between the effects of alcohol and the effects of THC. Alcohol leads to an increase in driving speed whereas THC leads to a decrease in speed. THC subjects drive in a more conservative manner, i.e., in the studies, they maintained a longer headway and refused more opportunities to pass, whereas the opposite was the case following alcohol. THC did, however, increase reaction time and the standard deviation of lateral position (SDLP), although the magnitude of impairment was generally small. There were also no significant interactions between alcohol and marijuana effects on performance, indicating that the combined effects of the drugs are additive.

A series of driving studies in actual traffic was conducted by a group of researchers at Maastricht University, The Netherlands. Robbe (1998) (Robbe 1998) investigated the effects of THC 0, 100, 200 and 300 µg/kg on performance in a one-hour road-tracking test and a thirty-minutes car-following test on a primary highway,

and the effect alcohol and THC 100 µg/kg on a city driving test. The combined effects of THC and alcohol were further investigated in two subsequent studies with subjects who were recreational users of marijuana. The first assessed the effects of THC 0, 100 and 200 µg/kg with and without a low dose of alcohol on road tracking and car-following performance (Ramaekers et al. 2000; Robbe 1998). In the second study, during a city driving test a licensed driving instructor used a standardized questionnaire to rate the effects of THC 0 and 100 µg/kg with and without a low alcohol dose (BAC <0.05 g/dl) on general driving proficiency (Lamers and Ramaekers 2001). In addition, the subjects' visual search for traffic at intersections was recorded by means of head-mounted cameras that registered the subject's eye and direction of gaze.

In these studies, THC produced a dose related increment in SDLP, which is a measure of "weaving", during the road-tracking test. Reaction time to the speed accelerations/ decelerations of a lead vehicle in the car-following test and general driving proficiency in the city driving test were not affected by THC. Blood concentrations of THC and THC-COOH were not related to the degree of impairment. The effects of THC on SDLP were comparable to those of alcohol at a BAC of 0.05 g/dl, the legal limit for driving in most European countries. THC in combination with a low dose of alcohol, however, produced severe performance impairment in the road-tracking test, and to lesser extents also in the car-following and city driving test. There were no significant interactions between alcohol and THC, indicating that the effects were additive. When compared to a previously established alcohol calibration curve (Louwerens et al. 1987), the combination of THC 100 and 200 µg/kg with alcohol produced a rise in mean SDLP equal to that associated with BACs of 0.09 g/dl and 0.14 g/dl, respectively.

Epidemiological studies have generally failed to establish an association between crash risk and driving under the influence of cannabis. Yet, most epidemiological surveys have established cannabis use among crashed drivers by determining the presence of an inactive metabolite of THC in blood or urine (Ramaekers et al. 2004). Unfortunately, this metabolite can be detected in body fluids for days after smoking and can only be taken as evidence for past use of cannabis. Recent use of cannabis can only be established by directly measuring THC in blood. The latter procedure was followed in only a few epidemiological surveys (e.g. (Drummer et al. 2004; Laumon et al. 2005). These surveys showed that THC positives are 2-6 times more likely to be responsible for their crash as compared to cases that had not used drugs or alcohol.

Significant odds ratios (OR) of crash risk for THC concentrations ranging between 1-2 ng/ml and 2-5 ng/ml in whole blood were 1.45 and 2.13 respectively (Laumon et al. 2005). At THC concentrations > 5 ng/ml in whole blood the ORs ranged from 2.1-6.6 (Drummer et al. 2004; Laumon et al. 2005). When converted to THC concentrations in serum their equivalents would be 2-4, 4-10 and >10 ng/ml respectively. These ranges correspond well with limits of impairment as established in a recent experimental study on the effect of THC on perceptual motor control, motor impulse control and cognition (Ramaekers et al. 2006b). In the latter study, slight and selective impairment of tracking performance was notable at THC ranges between 2-5 ng/ml, but impairments became truly prominent across all performance domains at serum THC concentrations between 5-10 ng/ml. These data support epidemiological data and show that THC serum concentrations between 2-5 ng/ml establish the lower and upper range of a per se limit for defining general performance impairment above which drivers are at risk.

In summary, experimental and epidemiological studies indicate that THC impairs driver ability and increases crash risk a dose-related manner. First indications of driver impairment and elevated crash risk in experimental and epidemiological studies were evident for serum THC concentrations > 2ng/ml.

HALLUCINOGENS

A wide variety of pharmacological substances produce so-called hallucinogenic effects. Briefly, a psychiatric definition of a hallucination is 'sensory perception without external stimulus of the relevant sensory organ' (DSM III-R 1987, American Psychiatric Association). In addition, the most important property of a hallucination is its illusory character, the hallucinant believes that the hallucination is a real perception. This should be distinguished from those which could be called hallucinatory experiences of which the percipient is aware that they are unreal. Drug-induced hallucinations are most often visual, such as geometric patterns or haloes around lights. Often, drug users are aware that these effects are produced by the substance taken, so that true drug-induced hallucinations are rare. Perhaps hallucinations induced by other medical conditions are less rare and should always be considered when encountering the problem in actual traffic. This could relate to schziophrenia (usually auditory hallucinations such as hearing voices), psychotic depression, pot-traumatic stress-disorder, fever, delirium, dementia, liver failure, kidney failure or brain cancer.

There are no systematic epidemiological studies of hallucinogen use by drivers or laboratory studies of the effects of hallucinogens on skills related to driving. Visual disturbances while driving, even more than ten hours after drug use, have been reported in individual cases (Woody 1970). Delayed visual hallucinations appearing days to months after the use of LSD potentially could impair driving capacity (Seppälä et al. 1979). High doses of stimulant drugs also frequently cause a sensation of bugs crawling on or immediately under the skin, which may have significant effects on behavior, in partular while driving.

Many substances that are discussed in other sections of this chapter, such as cannabis, amphetamines and MDMA, are said to possess hallucinogenic properties. This, however, appears not to be their primary characteristic. Therefore, this section focuses on substances, which are used primarily for their hallucinogenic effects. They are categorized according to their primary pharmacological mechanisms of action.

GLUTAMATERGIC HALLUCINOGENS (NMDA RECEPTOR ANTAGONISTS)

Phencyclidine (PCP) and ketamine are noncompetitive NMDA glutamate receptor antagonists. PCP can induce a broad range of psychological symptoms in non-schizophrenic subjects that resemble the symptoms observed in schizophrenia (Ellison 1995; Krystal et al. 1994; Oranje et al. 2000), including hallucinations, delusions, idiosyncratic and illogical thinking, poverty of speech and thought, agitation, disturbances of emotion, withdrawal, decreased motivation, and dissociation (Newcomer et al. 1999). Ketamine, a PCP analog still used in human anesthesia, has been reported to cause reactions similar to but not as severe as those caused by PCP, including brief, reversible “positive” and “negative” schizophrenia-like symptoms (Krystal et al. 1994; Newcomer et al. 1999). Both PCP and ketamine can exacerbate the psychosis in schizophrenia (Newcomer et al. 1999).

Ketamine

The most important adverse effects of the anaesthetic ketamine are hallucinations and excessive increases in blood pressure and heart rate (Moran 1999). These reactions can be attenuated or avoided by combining ketamine with sedative or hypnotic drugs (Adams and Werner 1997). A standard recreational dose of

ketamine is typically 1/8 g, usually taken intranasally, with effects lasting for approximately one hour. It is one of the drugs consumed regularly amongst members of the new dance culture. At present, the long-term consequences of ketamine use, including addictive potential, are not known (Moran 1999).

Subanaesthetic doses of ketamine can produce psychedelic effects in healthy volunteers. Several investigators have studied the effects of ketamine in volunteers to model cognitive deficits in schizophrenia, memory impairment and dementia. These studies have shown that NMDA antagonists produce a broad range of symptoms, behaviours, and cognitive deficits that resemble aspects of endogenous psychoses and thought disorder, particularly schizophrenia and dissociative states (Adler et al. 1998; Adler et al. 1999; Bowdle et al. 1998; Breier et al. 1997; Duncan et al. 2001; Hetem et al. 2000; Lahti et al. 2001; Van Berckel et al. 1998; Vollenweider et al. 1997a; Vollenweider et al. 1997b).

Phencyclidine

Phencyclidine (PCP) or "angel dust" is a dissociative anaesthetic with notoriety as an abuse substance. A derivative of the anaesthetic ketamine, PCP is the predominant member of the arylhexylamine class of designer drugs (Buchanan and Brown 1988). States of florid psychosis lasting for days can follow a brief encounter with PCP (Isaacs et al. 1986). Observations of many investigators have shown that the acute effects of PCP following several routes of administration are dose-related (Pradhan 1984). High doses produce acute intoxication with disturbing manifestations including psychosis, numbness, light-headedness, vertigo, ataxia, and nystagmus. Furthermore, some subjects in these studies became irritable, argumentative or negative under conditions of social stress and demanding tasks. In addition to a variety of central actions, PCP has also been shown to affect cardiovascular function, heat storage, and exercise performance. It can also induce, although rarely, psychotic episodes in psychotic and pre-psychotic personalities. Tolerance, but not physical dependence, develops to the effects of PCP. Psychological dependence as indicated by craving for the drug has, however, been reported. The elicitation of violent of psychotic behaviour by phencyclidine is well documented (Moran 1999).

SEROTONERGIC HALLUCINOGENS

The classical hallucinogens, such as LSD, DMT, mescaline or psilocibin, are all characterised by a serotonergic pharmacology; all display agonist activity at 5-HT_2 receptors, and there is evidence that some may interact with other 5-HT receptor subtypes as well, such as 5-HT_{1A} receptors (McKenna 1996). Chemically they tend to fall into one of three categories: phenylethylamine derivatives (mescaline and synthetic analogues), lysergamides (LSD, morning glory seeds) and tryptamine derivatives (psilocybin, psilocin, DMT) (McKenna 1996).

Lysergide

Lysergide (LSD), familiarly called "acid", is the synthetic version of ergotamine, produced by ergot, which is a parasite of rice or rye (Maes et al. 1999). It is the diethylamide of lysergic acid. After its discovery, LSD was misused very quickly for its hallucinogenic effects, because the active dose of this hallucinogenic is so small that the drug can be delivered in many forms, including microtablets, window pane, or stamps (Maes et al. 1999).

The most likely mechanism to account for LSD-induced hallucinations is the increase of neocortical glutamatergic neurotransmission through an initial partial agonistic action at 5-HT_2 receptors, predominantly 5-HT_{2A} receptors (Aghajanian and Marek 1999). The effects appear fifteen minutes to one hour after ingestion, and can last six to eight hours. Tolerance develops after only a few days of use. Cardiac frequency, blood pressure and temperature increase, and spatiotemporal distortion and depersonalization are frequently reported. Reaction time is significantly increased. Users can become so fearful that they will make suicide attempts. LSD induces a solid psychic dependence (Maes et al. 1999).

Magic mushrooms: psilocybin and psilocin

Magic mushrooms belong essentially to three groups: psilocybe, panaeolus and conocybe. The psychoactive hallucinogenic substances are psilocybin and psilocin, chemically similar to LSD. Effects can be obtained with 10 to 60 mg, and can last five to six hours. First, the user will be affected by nausea, and then sensations affecting eyes, hearing and consciousness occur. These products seem to induce less panic than LSD (Maes

et al. 1999), but their effects are similar. With psilocibin, 5-HT_{2A} agonism has been demonstrated as the mechanism to induce symptoms (Vollenweider et al. 1998b).

Ayahuasca (DMT)

Ayahuasca is a South American psychoactive beverage that contains the naturally occurring psychedelic agent N,N- dimethyltryptamine (DMT) (Riba et al. 2001). This "tea" has been used for centuries in religious and medicinal contexts in the rain forest areas of South America, and is presently gaining the attention of psychedelic users in North America and Europe. Tea brewed of encapsulated freeze-dried ayahuasca in a dose range of 0.5, 0.75, and 1.0 mg DMT/kg body weight, produces psychological effects including hallucinatory sensations. The effects begin within thirty to sixty minutes, peak between sixty and 120 minutes, and last until about 240 minutes. Ayahuasca effects are of longer duration and milder intensity than those previously reported for intravenously administered DMT. DMT and hence ayahuasca, like LSD, has affinity for 5-HT_{2A} receptors (Riba et al. 2001).

Mescaline (peyotecactus Lophophora Williamsii)

Mescaline is the active compound extracted from the peyote, a cactus from Central America. The chemical structure is 3,4,5-trimethoxy-phenethylamine. After oral ingestion, 66 percent can be absorbed (Maes et al. 1999). The effects are very similar to LSD, with reinforcement of color visions. Users call mescaline the “mellow LSD”, but real hallucinations are more frequent than with LSD. Tachycardia, hypertension, hyperthermia, hypersalivation and tremor are the most frequent side effects. Mescaline induces tolerance and psychic dependence, and may sometimes produce physical dependence (Maes et al. 1999). Synthetic derivatives of phenethylamine are substances like DOM (2,5-dimethoxy-4-methylamphetamine), and MDA (3,4-methylenedioxyamphetamine) that are structurally similar to the amphetamines (Christophersen 2000).

HALLUCINOGEN EFFECTS ON DRIVING PERFORMANCE

The incidence of the use of hallucinogens is not well documented. Taken from a database containing 44,000 records of persons registered in an addiction care unit in The Netherlands, it appeared that there were twenty-

nine cases reporting frequent LSD use. For comparison: 328 reported frequent use of MDMA (De Bruin et al. 1998).

There are no data from studies of hallucinogens effects on driving behaviour, but the many observations from experimental studies with healthy volunteers provide evidence that hallucinogen use and traffic participation do not mix in a safe manner. The reason for this is the primary motive for the use of hallucinogenic substances, which is the deliberate desire to experience an altered or distorted perception of reality.

INHALANTS

The term inhalants refers to a broad range of gases and vapors that can be inhaled to induce a psychoactive or mind-altering effect. Inhalants are inexpensive, readily available, and often abused by children, adolescents and young adults (Kurtzman et al. 2001). Based on their pharmacological and behavioral effects, they can be categorized in three main groups: (1) volatile solvents and fuels, (2) nitrous oxide and (3) alkyl nitrites (Balster 1998).

VOLATILE SOLVENTS AND FUELS

Volatile solvents are liquids that vaporize at room temperature. They are abundantly found in household and industrial products, including thinners, paint, nail polish remover, and correction fluids (acetone, toluene, methylene chloride, methanol), dry-cleaning fluids and degreasers (tetrachloroethylene, trichloroethane), gasoline and glues (toluene, hexane, ethyl acetate, trichloroethylene), and felt-tip marker fluids (toluene). Aerosols, including hairspray, deodorants and air fresheners, contain propellants (propane, butane, fluorocarbons [“freons”]), whereas paint and shoeshine sprays may contain solvents (toluene).

The majority of solvents have behavioral effects that are similar to that of the classic CNS depressants, i.e. alcohol, barbiturates and benzodiazepines (Balster 1998; Bowen et al. 1996a; Evans and Balster 1991). The neuronal mechanisms underlying the CNS effects have not yet been fully identified, but they may include enhancement of GABA and inhibition of NMDA neurotransmission (Balster 1998). Inhalation of solvents produces a very rapid intoxicated state that resembles alcohol intoxication in many respects (Bowen et al.

1996a; Bowen et al. 1996b; Sharp and Rosenberg 1997) including the psychomotor and cognitive effects (Echeverria et al. 1991). The symptoms include initial excitation turning to drowsiness, euphoria, disinhibition, lightheadedness and agitation. Increasing intoxication can lead to ataxia, slurred speech, delusions, dizziness and disorientation, and further intoxication may induce signs of sleeplessness, general muscle weakness, nystagmus and occasionally hallucinations (Dinwiddie 1994; Kurtzman et al. 2001; Sharp and Rosenberg 1997). In extreme cases, stupor typically develops and may progress to seizures, coma, cardiopulmonary arrest or, not uncommonly, death. Abusers may feel invulnerable and engage in high-risk, impulsive behaviors (Sharp and Rosenberg 1997).

Although intoxication is characterized by a rapid onset and equally rapid recovery, a ”high” can be maintained for several hours by repeated sniffing (Meredith et al. 1989). As a result, performance may be impaired for extended periods of time may thus present a safety hazard. To illustrate the potential risk, almost a quarter of related fatalities studied in Virginia were reported to be associated with sniffing while driving, riding or sitting in a motor vehicle (Bowen et al. 1999). Specific cases where car accidents were associated with the use of the propellant difluorethane (Broussard et al. 1997), the anaesthetic enflurane (Musshoff et al. 2002) and methylene chloride (Brewer et al. 1997) while driving have also been reported. Therefore, although no experimental data are available on solvent intoxication and driving capacity, impairment of performance that is qualitatively and quantitatively comparable to that of alcohol may be expected.

NITROUS OXIDE

Nitrous oxide or “laughing gas” is the most abused of the gases. Because nitrous oxide is commonly used as an analgesic in medicine and dentistry, medical personnel sometimes abuse it. It is also used as a propellant in whipped cream dispensers.

There is a wealth of information documenting that extended nitrous oxide inhalation (minutes to more than an hour), as used for anesthetic purposes, impairs psychomotor and cognitive functioning (Armstrong et al. 1995; Cheam et al. 1995; Fagan et al. 1994; File et al. 1992; Janiszewski et al. 1999; Walker and Zacny 2001; 2003; Zacny et al. 1994a; Zacny et al. 1999). A recent study compared effects on driving performance

in 20 knee arthroscopy surgery patients before and at 2h and 24h after general anesthesia using nitrous-oxide+oxygen to maintain anesthesia after induction with a number of other agents such as midazolam, propofol and fentanyl. Patients showed lower alertness levels and impaired driving skills preoperatively and 2 h postoperatively. Based on driving simulation performance and subjective assessments, authors concluded that patients are safe to drive 24 h after general anesthesia (Chung et al. 2005).

Nitrous oxide is most commonly abused via inhalation of higher concentrations for a very brief period of time (i.e., one or several breaths). The behavioral effects, including those on psychomotor performance, peak approximately thirty seconds after bolus inhalation and gradually subside over the time course of about five minutes. Nonetheless, even brief inhalation (four breaths) of 80 percent nitrous oxide has been shown to produce memory deficits as well as psychomotor impairment. Higher concentrations of nitrous oxide (100 percent) produce hypoxia, which may also add to the behavioral sequelae (Zacny et al. 1994b).

ALKYL NITRITES

Alkyl nitrites act primarily to dilate blood vessels and relax smooth muscle tissue through the release of endogenous nitric oxide. Most abused compounds are amyl nitrite (used medically for the treatment of angina), butyl nitrite and cyclohexyl nitrite. The latter is present in room odorizers, whereas amyl nitrite and butyl nitrite are sold in ampules or bottles and are called ”poppers”, “snappers” or “rush”. Alkyl nitrites are used as a euphoriant and as a sexual enhancer (Chalmers 1991). The use of nitric inhalants can acutely produce dizziness and headache from orthostatic hypotension. Nitrites increase global cerebral blood flow, and have been noted to decrease anger, fatigue and depression (Mathew et al. 1989). As with solvents and alcohol, biphasic effects on activity (activation followed by inactivation at higher dosages) are seen with amyl nitrite in animal studies (Bowen and Balster 1998). Users report a variety of short-term effects that are consistent with CNS depression, including lack of coordination and balance, blurred vision, short-term memory loss, and lethargy (French and Power 1997).

OPIOIDS

The opioids are a group of compounds that includes natural opium derivates (morphine and codeine), semisynthetic substances, the most notorious being heroin (diacetylmorphine), and synthetic drugs. The characteristics common to all opioids is that they exert their action by binding to specific opioid receptors, which are widely distributed throughout the brain and peripheral nervous system. Three main receptor subtypes have been identified; mu, delta and kappa receptors (Reisine and Pasternak 1996). Based on their affinity and actions on these receptors, opioids can be categorized into prototypical mu-agonists (morphine, heroin, methadone), partial mu-agonists (codeine) and mixed agonists-antagonists (buprenorphine) (Jaffe and Martin 1990; Zacny 1995).

Opioids are potent analgesics and opioid drugs are extensively used for the management of moderate to severe pain, and chronic pain in cancer patients (Breivik 2005; Joranson et al. 2000). They produce altered mood (often euphoria), decreased anxiety, respiratory depression, inhibition of gastrointestinal motility, inhibition of certain spinal reflexes, suppression of cough and a reduction of pupil size (miosis). They can also produce pruritus (itching), nausea and vomiting (Jaffe et al. 1997). The development of tolerance and physical dependence is a classic feature of all opioid drugs (Reisine and Pasternak 1996).

The primary opioid drug of abuse is heroin. However, among medical professionals who have readily access to them, other morphine-like agonists such as fentanyl and meperidine may also be abused. Methadone, a morphine-like agonist, is used to treat heroin abuse. Its longer action, availability as an oral preparation, and ability to blunt the craving for other opioids make methadone the most effective treatment for opioid abuse currently used.

The current general consensus with regard to the cognitive and psychomotor effects of opioids is that, while some impairment of performance may occur following a single administration, the debilitating effects soon wear off with continued administration of a fixed dose. Sudden dose increments may result in the temporary reappearance of impaired performance. For example, Bruera et al. (Bruera et al. 1989) demonstrated that after receiving their opioid medication (usually morphine or hydromorphone) cancer patients on stable opioid therapy experience no performance decrements, whereas patients who had a dose increment of at least 30 percent in the last three days showed impaired psychomotor, memory and arithmetic performance compared to pre-drug assessments.

Tolerance usually develops within days and sedative effects continue to decline within the first three weeks of opioid treatment (Kress and Kraft 2005). As a result, people who are on stable doses of opioids for an extended period of time, show little if any treatment-related cognitive impairment (Zacny 1995; Zacny 1996b). Patients who are on chronic opioid therapy, including methadone treatment for heroin abuse, are in principle considered fit to drive and work, (Byas Smith et al. 2005; Chapman 2001; Galski et al. 2000; Hanks et al. 1995; Kress and Kraft 2005; Smith 1996; Vainio et al. 1995; Zacny 1996a), although it is recommended that driver fitness is evaluated and monitored on a individual basis (Kress and Kraft 2005). In an extensive review of studies that have examined performance levels of patients on stable doses of opioids (Fishbain et al. 2003), it was concluded that the majority of studies indicated that opioids do not impair driving-related skills in opioid-dependent patients. Based on AHCPR (Agency for Health Care Policy Research) criteria, the evidence for no impairment was considered consistent for psychomotor functioning, actual driving performance (on/off road and simulators) and epidemiological data on stable opioid users and accident risk, motor vehicle violations and convictions. The evidence for cognitive impairment was inconclusive (Fishbain et al. 2003).

MORPHINE

Identification of the cognitive and psychomotor effects of opioid drugs is largely based on studies with morphine. A comprehensive review of these studies, dating back to the 1940s 1950s and 1960s, was published by Zacny (1995). In opioid-naive healthy volunteers, morphine in acute dosages up to 30 mg has been shown to impair a variety of functions, including reaction time, tracking, information processing, attention, and memory (Cleeland et al. 1996; Hanks et al. 1995; Walker and Zacny 1999; Zacny 1995; Zacny et al. 1998). This broad pattern of impairment is consistent with a mild dearousing effect (sedation), which is also apparent from subjective reports of mental clouding, confusion, grogginess and light-headedness. Generally, speed rather than accuracy is reduced (Zacny 1996a). It must be noted that the observed detrimental effects are generally very mild when compared, for example, to those of low dosages of benzodiazepines (Hanks et al. 1995), and most often performance is found to be unchanged (Hill and Zacny 2000; Walker and Zacny 1998; 1999; Zacny 1995; Zacny et al. 1998; Zacny et al. 1994c) or may even be

improved (O'Neill et al. 2000). As mentioned above, in opioid-dependent users the cognitive effects are even less pronounced as a result of tolerance (Zacny 1995). A recent report however suggests that even the milder slow release oral morphine as substitution treatment for heroin dependency produced significantly poorer psychomotor performance than methadone maintenance treatment. The authors stressed the preliminary status of these results but also pointed to its potential relevance because of the large number of maintenance treatment patients who drive (Giacomuzzi et al. 2005).

HEROIN

Given the highly addictive profile of heroin, major ethical objections prevent studies of it in an experimental setting. Hence, scant experimental data are available on the performance effects of heroin. Nevertheless, two remarkable studies conducted in the early 1960s describe the effect of both acute and sub-chronic administration of heroin in non-dependent opioid abusers (Fraser et al. 1963; 1964). The subjects were incarcerated men with a history of opioid abuse, but they were not dependent at the start of the experiment. In the two double-blind experiments, the subjects initially received placebo (saline) injections for thirty days (phase 1), with an exception of day seventeen, at which time saline was replaced by 8 mg heroin. Psychomotor (eye-hand coordination) performance was somewhat lower compared to the previous day, but performance on a twelve minute number cancellation task was not affected by the acute heroin administration. In the next phase, which lasted sixty days, the subjects received heroin four times a day in a incremental dosing regimen (10 to 95 mg) and became they physically dependent. During this time, psychomotor performance showed a small but significant decline in the first twelve days but returned to normal (phase 1) levels for the remainder of the study. These results demonstrate that, similar to other opioids, i.e. morphine, tolerance develops for the performance degrading effects of heroin.

The scantiness of experimental heroin studies allows no specific statement as to its performance effects. However, there is marked similarity between heroin and morphine in terms of their efficacy and at the mu-receptor, their ability to produce physical dependence. There also is similarity in their subjective, reinforcing and discriminative stimulus effects. Thus, one may predict minimal, if any, impairing effects of heroin in opioid-dependent users (Zacny 1995).

A recent report however suggests that even the milder slow release oral morphine as substitution treatment for heroin dependency produced significantly poorer psychomotor performance than methadone maintenance treatment. The authors stressed the preliminary status of these results but also pointed to its potential relevance because of the large number of maintenance treatment patients who drive (Giacomuzzi et al. 2005).

METHADONE

In a study by Curran et al (Curran et al. 2001), opioid dependent abusers who underwent a methadone treatment programme received their normal dose (10-50 mg) or a doubled dose according to a crossover design. Diminished long-term memory functioning was seen following the double dose but not the normal dose. Information processing, attention, and psychomotor speed remained unchanged. Reviewing the experimental data, Zacny (1995) concluded that orally administered doses used for methadone maintenance would not impair cognitive or psychomotor performance. Again, in nonusers (Rothenberg et al. 1977) and in users following a sharp dose increase, there is a greater risk of mild impairment.

Recent findings suggest that current methadone users do exhibit a reduction in certain cognitive functions compared to normal, non-drug abusing controls (Darke et al. 2000; Mintzer and Stitzer 2002; Specka et al. 2000). Since methadone maintenance patients typically have a history of prolonged (poly)drug abuse, it remains uncertain whether cognitive impairment is actually attributable to methadone treatment, or the result of for example structural brain damage due to prolonged opioid drug abuse, concomitant alcohol abuse or traumatic head injury. In an attempt to control for such confounding factors and hence assess the true effects of methadone therapy on cognition, Vendejo et al. (2005) compared former heroin abusers with and without methadone maintenance treatment. In this study, methadone maintenance patients showed impaired performance on tests of processing speed, visuo-spatial attention, cognitive flexibility, working memory and analogical reasoning. The authors conclude that methadone consumption itself may impair executive functioning and processing speed (Verdejo et al. 2005).

A recent study compared the effects of the methadone, buprenorphine and levo-alpha-acetyl-methodol (LAAM), as used in maintenance pharmacotherapy for heroin dependence, upon simulated driving with and

without alcohol in 3 months stabilized clients and a control group of non-drug-using participants. While alcohol impaired all measures of driving performance, there were no differences in driving skills across the four participant groups. These findings suggest that typical community standards around driving safety should be applied to clients stabilized in methadone, LAAM and buprenorphine treatment. The findings were considered to be important in terms of the widespread implementation of these treatment options in Victoria, Australia, given that a large proportion of pharmacotherapy clients drive (Lenne et al. 2003). These results are somewhat at odds with those of 2 studies reporting that the newer buprenorphine treatment produces significantly less psychomotor and cognitive impairment as measured with tests capturing driving skills, than methadone treatment in heroin dependence patients (Schindler et al. 2004) (Soyka et al. 2005).

In conclusion, impairment of cognitive ability by opioid drugs is not necessarily or specifically linked to absolute dosage levels. Although there appears to be a rather straightforward dose-response relation in drug-naive users (Walker and Zacny 1999; Zacny et al. 1994c), prolonged opioid users become insensitive to the adverse cognitive effects of even quite high fixed doses (Zacny 1995), although some residual impairment may persist. In the practical setting of drug abuse, however, opioid doses for an individual are likely show considerable variation. Heroin content may vary greatly from dose to dose and the prevalence of nonlethal heroin overdose is extremely high (McGregor et al. 1998). This incidental exposure to higher than normal dosages is likely to produce diminished psychomotor and cognitive abilities. Also, in certain specific situations impairment by occur despite apparent habituation. For example under conditions of low light, the miotic effect to which no tolerance develops (Reisine and Pasternak 1996), may impair performance that is dependent on visual acuity, such as night driving. Furthermore, opioids are known to alter mood, attitude and most likely risk assessment, changes which may ultimately result in careless, indifferent and risky behaviour and increase the likelihood of traffic accidents. Epidemiological data, however, do not indicate that opioid use is associated with increased accident risk (Fishbain et al. 2003; Zacny 1995). This supports the notion that stable doses are safe and may indicate that those who abuse opioid are not likely to engage in traffic.

GAMMA HYDROXYBUTYRIC ACID

Gamma hydroxybutyric acid (GHB) is a substance akin to Gamma-Amino-Butyric-Acid (GABA) that is naturally present in mammal species. It is used as an anaesthetic agent, but other indications have been suggested, such as the treatment of insomnia, alcohol and opiates withdrawal, and many cerebrovascular disorders. After oral absorption, the GHB peak is reached in serum after twenty to forty-five minutes, and the half-life is proportional to the amount ingested (more or less twenty minutes). Metabolism occurs in the liver with oxidation in CO_2. Urinary elimination is very limited (1 to 5 percent of the absorbed quantity) (Maes et al. 1999).

GHB is abused for its euphoric, sedative and anabolic (bodybuilding) effects. An "amphetamine like" sensation is obtained after 20 to 30 mg/kg, and with 10 mg/kg, amnesia and muscular relaxation can be observed. GHB is abused for its euphoric effects and is also reported to increase muscle mass and sexual pleasure (Bosman and Lusthof 2003). These properties have led to its use as a rape drug. Physical dependence occurs. Side effects are nausea, vomiting, vertigo, sleepiness, bradycardia, and respiratory depression. Coma and seizures have been reported following GHB abuse. Patients regain consciousness spontaneously within a few hours after ingestion. Ingestion in combination with alcohol or other psychoactive drugs is very dangerous. One of the major concerns with GHB is the narrow range between dosage needed for desired effects and dosage resulting in loss of consciousness or even coma.

In one study, the effects of GHB on human psychomotor performance and subjective feelings important for the safety of skilled performance, such as driving, were investigated (Ferrara et al. 1999). After single doses of 12.5 and 25 mg/kg (therapeutic doses in alcohol addiction treatments), GHB did not induce changes in psychomotor performance and, therefore, the drug did not seem to influence the ability to drive or work (Ferrara et al. 1999). However, repeated reports of the abuse potential of GHB and its use in treating ethyl alcohol addiction indicate that it may play an "agonist-like" role, which means that it should only used under close medical supervision (Ferrara et al. 1999).

A recent study of forensic GHB cases in The Netherlands (blood >5mg/l and urine >10mg/l) included amongst cases of chemical submission (rape drug), cases of driving under the influence (Bosman and Lusthof 2003). GHB was found in 13 cases of driving under the influence. In contrast to the cases of chemical submission, high concentrations of GHB were found, corresponding with observations of extreme

sleepiness or temporary loss of consciousness. Authors expressed their concerns that use of GHB in traffic may be underestimated because its incidence cannot be derived from present routine toxicological data (Bosman and Lusthof 2003).

Couper & Logan (2004) describe a case of a 38 year old man who has been arrested 7 times over an 8 month period for driving under the influence of GHB. Blood GHB concentrations ranged from 44 to 184 mg/L (N = 7, mean 100 mg/L, median 73 mg/L). Overall signs of impairment included erratic driving (severe lane travel, collisions, and near-collisions), slurred speech, disorientation, slow to react, shaking, agitation, unable to focus, poor coordination and balance, poor performance in field sobriety tests, somnolence, and unconsciousness. Despite the single-case aspect, this study provided clear insight that documented concentration ranges of GHB and its analogs are capable of causing severe cognitive and psychomotor impairment and their use is contraindicated for the safe operation of a motor vehicle (Couper and Logan 2004).

CONCLUSIONS

Without exception, all illicit drugs have the potential to impair the cognitive and behavioural skills that allow a person to engage in normal daily activities, such as driving and working. A person's ability to interact optimally with the environment may be compromised by a distorted perception of the world due to the effects of hallucinogens, marijuana or psychostimulant drugs. Miotic or mydriatic effects of opioids and psychostimulants, respectively, prevent optimal adaption to changing environmental light intensities. On a more general level, drugs such as opioids and inhalants produce CNS depressant effects and may cause sedation, leading to reduced accuracy and responsivity as well as overall dysfunction over a wide range of cognitive domains. In contrast, psychostimulants can induce a state of over-activation in which premature and inaccurate responding may occur. In addition, most drugs produce mood and attitude changes, diminish a person's judgment, quality of decision-making and risk assessment, and produces disinhibition. Most notable are the feelings of overconfidence and increased aggression following stimulant abuse and consequent exposure to risky and dangerous situations. Thus, despite their apparent performance-enhancing effects in certain controlled laboratory task, stimulants are likely to reduce performance in real life.

If, and to what extent, impairment will actually occur with a drug is dependent of certain additional factors besides its potential behavioural effects. Drug dosage, of course, is an important determinant as many behavioural effects are dose-dependent. However, the development of tolerance or sensitisation, or metabolic differences leading to unusually high or low blood drug levels, can modify an individual's response to a particular dose. Environmental cues, i.e. the context in which the drug is used, may also play an important role.

It must also be noted that the dosage and purity of a street drug is often unclear, and illicit drug formulations may contain numerous, potentially toxic constituents, the combined effects of which are largely unknown. Furthermore, poly-drug use is a common rather than exceptional practice among drug abusers. Interaction effects between various illicit drugs, as well as co-use of alcohol, can produce additive and potentiated behavioural effects, which are often not investigated and thus are unknown.

Finally, there is a surge of recent studies reporting presence or absence of effects on driving performance by using driving simulators or laboratory tasks mimicking driving skills. We would like to caution for the risk that these studies may indice a false sense of security when they conclude that certain substances do not impair driving simulator performance or psychomotor skills relevant for driving. Although these studies are important as a preliminary screen of the potential for impairing functions that are a prerequisite for driving capacity, they can not be taken to draw firm conclusions about driving impairment, traffic safety or accident risk itself, more than by proxy. For all these reasons mentioned, there is still a need to conduct controlled studies of drug exposure and effect on driving performance in actual traffic.

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