Driving Under the Influence of Non-Alcohol Drugs — An Update. Part II: Experimental Studies

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ABSTRACT: Experimental studies on the impairing effects of drugs of relevance to driving-related performance published between 1998 and 2015 were reviewed. Studies with on-the-road driving, driving simulators, and performance tests were included for benzodiazepines and related drugs, cannabis, opioids, stimulants, GHB, ketamine, antihistamines, and antidepressants. The findings in these experimental studies were briefly discussed in relation to a review of epidemiological studies published recently. The studies mainly concluded that there may be a significant psychomotor impairment after using benzodiazepines or related drugs, cannabis, opioids, GHB, or ketamine. Low doses of central stimulants did not seem to cause impairment of driving behavior.

KEYWORDS: Amphetamines, benzodiazepines, cannabis, cocaine, drugged driving, DUID, experimental, hypnotics, impairment, impaired driving, opioids.

INTRODUCTION

A review article on the effect of non-alcohol drug use on traffic safety was published in this journal in 2000 [68]. The article included experimental and epidemiological studies published before 1998 for the following drug groups: benzodiazepines and related drugs, cannabis, opioids, amphetamine and related drugs, antihistamines, and antidepressants. Many investigations have been performed since then. We have presented an update of epidemiological studies in a recent issue of this journal [34]. In the present article, experimental studies on the acute effects of drugs on psychomotor and cognitive performance as well as actual and simulated driving performance published between 1998 and 2015 are reviewed.

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

There are, however, a number of advantages with experimental investigations compared with epidemiological studies. First, several factors that may interfere with drug-related effects can be controlled for or excluded, such as age, gender, driving experience, health, exhaustion or sleepiness, the concomitant use of other psychoactive substances, previous or current drug abuse problems, risk-taking personality, criminal behavior, etc.; second, several types of cognitive and psychomotor functions that are relevant for safe driving may be studied, such as automative behavior (i.e., well-learned, automatic action patterns), control behavior (controlled action patterns), and executive planning behavior (interaction with ongoing traffic); third, well-documented, validated standardized tests may be used so that findings can be compared with other, similar studies [84]. Recommendations for experimental research on drugs and driving have been published [112].

Another type of study, which may be regarded as "semi-experimental", (*see* section I-E) is the study of psychomotor performance by drug users who have recently been taking a psychoactive drug *ad libitum*, either for therapeutic or recreational purposes, usually after previous drug use for an uncontrolled length of time, and therefore have varying experience and degree of tolerance to the drug in question. Such studies are, for example, those where drivers suspected of impaired driving are subjected to an examination by a neutral observer (e.g., a physician) at the time when a blood sample is drawn for drug analysis. In some countries this is standard procedure, and some publications have emerged on the relation between blood drug concentration and observed impairment. This type of studies has been included in the present review as they have some similarities to experimental studies of acute drug effects.

The present article is an update of a previous review of studies performed before 1998 [68]. We have therefore included experimental studies published during 1998–2015 for different psychoactive drugs.

I. METHODOLOGICAL ISSUES

A. Data Sources and Search Strategy

A broad search of the English-language literature was performed incorporating both electronic and manual components. The electronic search was performed using PubMed.

The principal inclusion criteria for experimental studies on the impairing effects of drugs of relevance to driving were:

- Laboratory tests of traffic relevance (i.e., measuring sedation, drowsiness, divided attention, continuous perceptual-motor coordination, speed and accuracy of decision making, vigilance, and short-term memory) or on-the-road driving or driving simulator test;
- Alcohol as reference drug;
- Pharmacokinetic data;
- More than eight participants; and
- Published in 1998 or later.

For some drugs we were not able to retrieve any studies complying with the above criteria, and in such cases, additional studies were included according to following criteria:

- Studies without a reference drug, but testing "standard deviation of lateral position" (SDLP) in real life or in a driving simulator, and some studies with simulated driving without SDLP;
- Studies using other drugs than alcohol as "reference" drug where indirect comparison of impairment can be made; and
- Studies without pharmacokinetic data, but where the blood drug concentrations can be estimated from the information given (drug dose and time).

The search included the following drugs: alprazolam; amphetamine; antidepressants; antihistamines; buprenorphine; clonazepam; cocaine; codeine; diazepam; fentanyl; flunitrazepam; GHB; ketamine; MDMA (Ecstasy); methadone; methamphetamine; methylphenidate; morphine; nitrazepam; oxazepam; oxycodone; phenazepam; THC (tetrahydrocannabinol); tramadol; zolpidem, and zopiclone. The drugs were selected based on a previous review article on the effect of drug use on traffic safety published in this journal in 2000 [68]. The studies included in this review are presented in **Table 1**.

In addition to the experimental studies, this review also includes a number of studies of clinical signs of impairment after *ad libitum* intake (semi-experimental studies). An electronic search for published studies describing the relationship between drug concentrations in blood and the outcome of a clinical test of impairment (CTI) was also performed using PubMed. The principal inclusion criteria were:

- Drug was used *ad libitum*;
- Analysis of alcohol and a wide range of psychoactive drugs in blood samples;
- Only one drug detected in the blood sample;
- Performance of a CTI when collecting blood sample; and
- Published in 1998 or later.

Table 1. Experimental studies

Drug; adm.; dose[a]	Test following drug adm.	Subject no. (m/f); age; status[b]	Pharmacokinetics[a,c]	Metho-dology[d]	Test	Effect[e]	Control[f]	Bio. sample analyzed[g]	Ref.
Alprazolam; po; IR/XR; 1 mg	1–5.5 h (task) 4–5 h (driving)	18 (9/9); 20–45 year; HV	Mean serum conc.: 4.9 ng/mL (IR) 1.7 ng/mL (XR) (55 min)	Co, Db, Pc, Rd	Actual driving; Cognitive/psychomotor performance	Y	P	N	[62]
Alprazolam; po; 1 mg	1 h (driving) 2.5 h (task)	20 (8/12); 25.1±2.0 year; HV	N	Co, Db, Pc, Rd	Actual driving; Cognitive/psychomotor performance	Y	P	Br, U	[108]
Amphetamines (*d,l*-MA); 0.42 mg/kg	2.5 h	20 (10/10); 21–34 year; Healthy recreational illicit stimulant user	Mean blood conc.: 90 ng/mL (120 min) 95 ng/mL (170 min) 105 ng/mL (240 min)	Db, Pc	Simulated driving	N	P	N	[87]
Amphetamines (*d,l*-MA); po; 0.42 mg/kg	3–4 h	20 (10/10); 21-34 year; HV	Mean blood conc.: 90 ng/mL (120 min) 95 ng/mL (170 min) 105 ng/mL (240 min)	Db, Pc	Cognitive/psychomotor performance	Y/N/↑	P	N	[89]
Amphetamines (*d*-A); 10 mg (LD) 40 mg (HD)	1.5–11.5 h	18 (18/0); 23–34 year HV	Plasma Cmax: 40 ng/mL (LD) 140 ng/mL (HD)	Co, Db, Pc, Rd	Simulated driving	↑	P	Br, U	[45]
Amphetamines (*d*-A); po; 0.42 mg/kg	120 min	20 (10/10); 21–32 year; HV	Mean blood conc.: 83 ng/mL (120 min) 98 ng/mL (170 min)	Db, Pc	Simulated driving	Y	P	N	[90]

Table 1. (Continued)

Drug; adm.; dose[a]	Test following drug adm.	Subject no. (m/f); age; status[b]	Pharmacokinetics[a,c]	Metho-dology[d]	Test	Effect[e]	Control[f]	Bio. sample analyzed[g]	Ref.
Amphetamines (*d*-A); po; 0.42 mg/kg	3–4 h	20 (10/10); 21–32 year; HV	Mean blood conc.: 83 ng/mL (120 min) 98 ng/mL (170 min) 96 ng/mL (240 min)	Db, Pc	Cognitive/psychomotor performance	Y/N/↑	P	N	[89]
Amphetamines (*d*-A); po; 10 mg	120–170 min	18 (12/4); 21–37 year; Infrequent user of alcohol & ampheta-mine-like substances	Blood conc.: 20.8 (11.9–39.1) ng/mL (120 min)	Co, Db, Pc, Rd	Simulated driving; Cognitive/psychomotor	N	Alc, P	Br, U	[92]
Amphetamines (*d*-MA); po; 0.42 mg/kg	3–4 h	20 (10/10); 21–32 year; HV	Mean blood conc.: 72 ng/mL (120 min) 67 ng/mL (170 min) 59 ng/mL (240 min)	Db, Pc	Cognitive/psychomotor performance	Y/N/↑	P	N	[89]
Amphetamines (*d*-MA); po; 0.42 mg/kg	2.5 h	20; 21–32 year; Healthy recreational illicit stimulant user	Mean blood conc.: 72 ng/mL (120 min) 67 ng/mL (170 min) 59 ng/mL (240 min)	Db, Pc	Simulated driving	N	P	N	[88]
Amphetamines (*d*-MA); po; 0.42 mg/kg	3 h 24 h	61 (28/33); 21–34 year; Abstinent recreational drug user	Peak blood conc.: 91.65 ng/mL (3 h)	Db, Pc	Cognitive/psychomotor performance	Y/N/↑	P	B	[94]
Amphetamines (MA); po; 10 mg	1.75–8.25 h	9 (9/0); 34–47 year; Stimulant & alcohol user	N	Db, Pc	Cognitive/psychomotor performance	N	Alc, P	N	[53]
Amphetamines (MA); po; 20 mg (LD) 40 mg (HD)	1–6.75 h	11 (9/2); 29.3±5.0 year; Previous experience with MA & MDMA	Peak plasma conc.: 50 ng/mL (LD) 120 ng/mL (HD) (3 h)	Co, Pc	Cognitive/psychomotor performance	N/↑ (dd)	P	N	[54]
Amphetamines (MA); po; 0.42 mg/kg	3+24 h	61 (28/33); 21–34 year; Abstinent recreational drug user	Peak blood conc.: 91.65 ng/mL (3 h)	Db, Pc	Simulated driving	Y	P	B	[93]
Cocaine; po; 300 mg	15–60 min	61 (48/13); 18–32 year; Heavy cannabis user with cocaine use history	Mean serum conc.: 284±198 ng/mL (50 min)	Co, Db, Pc	Cognitive/psychomotor performance	Y/N/↑	P	Br, U	[98]
Codeine; po; 20 mg (LD) 40 mg (MD) 60 mg (HD)	1-4 h	16 (8/8); 22.4±2.7 year; HV	Mean serum conc.: 18.26±14.01/6.12±16.46 ng/mL (LD) 31.85±21.28/43.62±13.07 ng/mL (MD) 40.33±34.37/57.12±19.41 ng/mL (HD) (1 h/4 h)	Co, Db, Pc, Rd	Simulated driving; Cognitive/psychomotor performance	Y/N	P		[3]
Codeine; po; 30 mg	1-4 h	24 (24/0); 24±3 year; HV	N	Co, Db, Rd	Cognitive/psychomotor performance	Y/N	B	N	[73]
Diazepam; po; 15 mg	1–5 h	12 (7/5); 21–28 year; HV	Mean plasma conc.: 342 ng/mL (1.5 h)	Co, Db, Pc, Rd	Simulated driving; Cognitive/psychomotor performance	Y/N	Alc, B, P	N	[67]
Diazepam; po; 1.5 mg	1.5+4 h	9 (6/3); 22–24 year; HV	Mean plasma conc.: 0.27 ng/mL (2 h)	Co, Db, Pc	Simulated driving; Cognitive/psychomotor performance	Y	Alc, B, P	N	[99]
Diazepam; po; 10 mg	1.5 h 4 h	9 (5/4); 55–77 year; HV	Mean plasma conc.: 0.21 ng/mL (2 h)	Co, Db, Pc	Simulated driving; Cognitive/psychomotor performance	Y/N	Alc, B, P	N	[99]
Fentanyl; inj; 0.2 µg/kg	15 min	24 (24/0); 27.3±4.92 year; HV	Plasma conc.: 1.91 (27.3±1.17) ng/mL (15 min)	Co, Pc, Rd	Cognitive/psychomotor performance	Y/N	Alc, P	N	[85]

Table 1. (Continued)

Drug; adm.; dose[a]	Test following drug adm.	Subject no. (m/f); age; status[b]	Pharmacokinetics[a,c]	Metho-dology[d]	Test	Effect[e]	Bio. sample Control[f]	Bio. sample analyzed[g]	Ref.
Flunitrazepam; po; 1.25 mg	0.25–6 h	12 (12/0); 22–33 year; Recreational GHB user	Cmax mean plasma conc.: 14.5 ng/mL (Peak between 15–90 min)	Co, Db, Pc, Rd	Cognitive/psychomotor performance	Y	Alc, B, P	Br, U	[1]
Flunitrazepam; po; 1 mg	10 h	16 (8/8); 55–65 year; HV	Mean serum conc.: 1.6 (1.0–2.4) ng/mL (9.5 h) 1.3 (1.5–2.8) ng/mL (14.5 h)	Co, Db, Pc, Rd	Simulated driving	N	P	U	[12]
GHB; po; 40 mg/kg (LD) 60 mg/kg (HD)	0.25–6 h	12 (12/0); 22–33 year; Recreational GHB user	Cmax mean plasma conc.: 111±37.4 µg/mL (LD) 166.9±48.4 µg/mL (HD) (Peaked between 30–90 min)	Co, Db, Pc, Rd	Cognitive/psychomotor performance	Y (dd)	Alc, B, P	Br, U	[1]
GHB; po; 12.5 mg/kg (LD) 25 mg/kg (HD)	15–180 min	12 (6/6); 22–36 year; HV	N	Co, Db, Pc, Rd	Cognitive/psychomotor performance	N	B, P	N	[30]
GHB; po; 1-10 g/70 kg	0.5–24 h	14 (11/3); 21–50 year; Sedative abuse history	N	Db, Pc	Cognitive/psychomotor performance	Y(dd)/N	Alc, B, P	N	[47]
Ketamine; im; 0.2 mg/kg 0.4 mg/kg	5–10 min 125 min	20 (10/10); 19–42 year; HV	N	Co, Db, Pc	Cognitive/psychomotor erformance	Y/N	B, P	Br, U	[20]
Ketamine; iv; 0.26 mg/kg bolus + 0.65 mg/kg per h	5–180 min	23; 31.3±2.9 year; HV	Plasma conc.: 200 ng/mL	Db, Pc, Rd	Cognitive/psychomotor performance	Y (dd) /N	B, P	U	[56]
Lorazepam; po; 0.03 mg/kg	15–180 min	12 (6/6); 23–36 year; HV	N	Co, Db, Pc, Rd	Cognitive/psychomotor performance	Y	B, P	N	[30]
Lorazepam; po; 2 mg	5–180 min	23; 31.3±2.9 year; HV	Peak plasma conc.: 19 ng/mL (15 min)	Db, Pc, Rd	Cognitive/psychomotor performance	Y/N	B, P	U	[56]
Lorazepam; po; 2 mg	15–300 min	18 (9/9); 24.1±2.6 year; HV	N	Co, Db, Pc, Rd	Cognitive/psychomotor performance	Y	B, P	Br, U	[113]
MDMA; po; 25 mg (LD) 50 mg (MD) 100 mg (HD)	2–4 h 12–14 h (no sleep)	16 (8/8); 22 year (mean); Recreational MDMA user	Mean serum conc.: 25.8±3.3 ng/mL (LD) 64±6.4 ng/mL (MD) 157±9.5 ng/mL (HD) (1.5 h)	Co, Db, Pc, Rd	Actual driving	N	P	Br, U	[14]
MDMA; po; 100 mg	30–360 min	16 (9/7); 18–29 year; Regular Ecstasy user	Cmax plasma: 202.5±74.1 ng/mL (150 min)	Co, Db, Pc, Rd	Cognitive/psychomotor performance	N/↑	Alc, B, P	U	[28]
MDMA; po; 100 mg	15–300 min	16 (12/4); 18–27 year; Regular Ecstasy user	Mean Cmax plasma: 213 ng/mL (105 min)	Co, Db, Pc, Rd	Cognitive/psychomotor performance	Y/N	B	U	[29]
MDMA; po; 100 mg	1–6.75 h	11 (9/2); 29.3±5.0 year; Previous experience with MA & MDMA	Peak plasma conc.: 220 ng/mL (3 h)	Co, Pc	Cognitive/psychomotor performance	N	P	N	[54]
MDMA; po; 75 mg (LD) 100 mg (HD)	1.5–2 h (task) 3–5 h (driving)	18 (9/9); 26.6±5.4 year; Recreational MDMA user	Blood conc.: 137.4±31.9 ng/mL (LD) 191.8±49.1 ng/mL (HD) (1.5 h)	Co, Db, Pc, Rd	Actual driving; Cognitive/psychomotor performance	N/↑	Alc, P	Br, U	[57]
MDMA; po; 75 mg	3–5 h	18 (9/9); 21–39 year; MDMA user	Mean plasma conc.: 113.4±37.4 ng/mL (3 h)	Co, Db, Pc, Rd	Actual driving	Y/↑	P	Br, U	[77]
MDMA; po; 100 mg	3 h 24 h	61 (28/33); 21–34 year; Abstinent recreational drug user	Peak blood conc.: 203.11 ng/mL (3 h)	Db, Pc	Simulated driving	Y	P	B	[93]

Table 1. (Continued)

Drug; adm.; dose[a]	Test following drug adm.	Subject no. (m/f); age; status[b]	Pharmacokinetics[a,c]	Metho-dology[d]	Test	Effect[e]	Control[f]	Bio. sample analyzed[g]	Ref.
MDMA; po; 100 mg	3 h 24 h	61 (28/33); 31–34 year; Abstinent recreational illicit drug user	Peak blood conc.: 203.11 ng/mL (3 h)	Db, Pc	Cognitive/psychomotor performance	Y/N	P	B	[94]
MDMA; po; 100 mg	1.5–3.5 h	19 (10/9); 21–40 year; HV using alcohol	Average (SD) blood conc.: 170.41 (160.22) ng/mL (1.5 h)	Co, Db, Pc, Rd	Simulated driving	↑	Alc, P	Br, U	[101]
Morphine; po; 40 mg	15–300 min	18 (9/9); 24.1±2.6 year; HV	N	Co, Db, Pc, Rd	Cognitive/psychomotor performance	N	B, P	Br, U	[113]
MPH; po; 20 mg	3-5 h	18 (9/9); 21–39 year; Recreational MDMA user	Mean plasma conc.: 95.9±78.4 ng/mL (ritalinic acid) (3 h)	Co, Db, Pc, Rd	Actual driving	N/↑	P	Br, U	[77]
Oxazepam; po; 30 mg	1–5 h	12 (7/5); 21–28 year; HV	Mean plasma conc.: 190 ng/mL (1.5 h)	Co, Db, Pc, Rd	Simulated driving Cognitive/psychomotor performance	Y/N	Alc, B, P	N	[67]
Oxycodone; po; 5 mg (LD) 10 mg (HD)	1 h (driving) 2.5 h (task)	18 (6/12); 24.0±1.6 year; HV	N	Co, Db, Pc. Rd	Actual driving; Cognitive/psychomotor performance	Y (dd)/N	P	Br, U	[104]
Oxycodone; po; 10 mg (LD) 20 mg (HD) 30 mg (HD)	15–300 min	18 (9/9); 24.1±2.6 year; HV	N	Co, Db, Pc, Rd	Cognitive/psychomotor	Y (dd)/N	B, P	Br, U	[113]
Oxycodone; po; 10 mg	60–360 min	14 (8/6); 26.7±4.7 year; HV	N	Co, Db, Pc, Rd	Cognitive/psychomotor performance	N	B, P	Br, U	[114]
Temazepam; po; 20 mg	10–11 h (driving) 8.75–9.5 (task)	18 (8/10) (task); 55–75 year; HV	N	Co, Db, Pc, Rd	Actual driving; Cognitive/psychomotor performance	Y/N	P	N	[61]
THC; inh; 1.8% (LD) 3% (HD)	25 min	80 (49/31); 21–35 year; Recreational (regular & nonregular) cannabis & alcohol user	Plasma conc. (mean±SD): Pre-drive, 73.46±37.36 ng/mL (LD) 90.06±38.65 ng/mL (HD); Post-drive, 38.20±15.86 ng/mL (LD) 44.90±17.90 ng/mL (HD)	Db, Pc	Simulated driving	Y	Alc, P	B	[25]
THC; inh; 4+6+6 mg 90 min interval	15–300 min	16 (12/4); 18–27 year; Regular Ecstasy user	Mean plasma conc.: 4 mg, 59.7±5.6 ng/mL; 6 mg (1st), 74.8±6.9 ng/mL 6 mg (2nd), 74.8±6.9 ng/mL (5 min)	Co, Db, Pc, Rd	Cognitive/psychomotor performance	Y/N	B, P	U	[29]
THC; inh; 19 mg (LD) 38 mg (HD)	5 min	25 (exp'ed driver) 22 (inexp'ed driver); 25–40 year	Blood conc.: 7.4±3.87 ng/mL (LD) 12.01±5.53 ng/mL (HD) (25 min)	Co, Db, Pc	Simulated driving	Y (dd)	Alc, P	N	[60]
THC; inh; 100 µg/kg 200 µg/kg	30 min	18 (9/9); 20–28 year; Current cannabis & alcohol user	N	Co, Db	Actual driving	Y/N	Alc, P	Br, U	[78]
THC; inh; 400 µg/kg	20–200 min	21 (15/6); Heavy cannabis user	Mean serum conc.: 112.1±47.5 ng/mL (15 min)	Co, Db, Pc	Cognitive/psychomotor performance	Y/N	Alc, B, P	U	[79]
THC; inh; 13 mg (LD) 17 mg (HD)	30–58 min	14 (10/4); 26.1±1.3 year; Recreational alcohol & cannabis user	N	Co, Db, Pc	Simulated driving	Y (dd)/N	Alc, B, P	N	[83]

Table 1. (Continued)

Drug; adm.; dose[a]	Test following drug adm.	Subject no. (m/f); age; status[b]	Pharmacokinetics[a,c]	Metho-dology[d]	Test	Effect[e]	Control[f]	Bio. sample analyzed[g]	Ref.
THC; inh; 13 mg	15–80 min	12 (7/5); 24–29 year; Recreational alcohol & cannabis user	N	Co, Db, Pc	Simulated driving; Cognitive/psychomotor performance	Y	Alc, B, P	N	[82]
THC; inh; 300 µg/kg	15–60 min	61 (48/13); 18–32 year; Heavy cannabis user with cocaine use history	Mean serum conc.: 55.3±29.5 ng/mL (5 min)	Co, Db, Rd	Cognitive/psychomotor performance	Y	P	Br, U	[98]
Tramadol; po; 37.5 mg	60-240 min	24 (24/0); 24±3 year; HV	N	Co, Db, Rd	Cognitive/psychomotor performance	N	B	N	[73]
Triazolam; po; 0.2 mg/70 kg 0.4 mg/70 kg	80–200 min	20 (10/10); 19–42 year; HV	N	Co, Db, Rd	Cognitive/psychomotor performance	Y	B, P	Br, U	[20]
Zolpidem; po; 15 mg	10 h	16 (8/8); 55–65 year; HV	Mean serum conc.: 95.4 (15–240) ng/mL (9.5 h) 54.7 (15–225) ng/mL (14.5 h)	Co, Db, Pc, Rd	Simulated driving	Y	P	U	[12]
Zolpidem; po; 15 mg	1–5 h	12 (7/5); 21–28 year; HV	Mean plasma conc.: 196 ng/mL (1.5 h)	Co, Db, Db, Rd	Simulated driving; Cognitive/psychomotor	Y	Alc B, P	N	[67]
Zolpidem; po; 10 mg (LD) 20 mg (HD)	4 h	30 (15/15); 24±2.4 year; HV	N	Co, Db Pc	Actual driving; Cognitive/psychomotor performance	Y (dd)	Alc, P	Br	[107]
Zopiclone; po; 7.5 mg	1–5 h	12 (7/5); 21–28 year; HV	Mean plasma conc.: 93 ng/mL (1.5 h)	Co, Db, Pc, Rd	Simulated driving; Cognitive/psychomotor performance	Y/N	Alc, B, P	N	[67]
Zopiclone; po; 7.5 mg	10 h	16 (8/8); 55–65 year; HV	Mean serum conc.: 25.4 (18–33) ng/mL (9.5 h) 11.7 (2–23) ng/mL (14.5 h)	Co, Db Pc, Rd	Simulated driving	Y	P	U	[12]
Zopiclone; po; 5 mg (LD) 10 mg (HD)	1–6.5 h	16 (16/0); 20–28 year; HV	Mean blood Cmax: 26±2 ng/mL (LD) 50±3 ng/mL (HD) (1.7 h)	Co, Db, Pc, Rd	Cognitive/psychomotor performance	Y	Alc, B, P	U	[38]
Zopiclone; po; 5 mg 10 mg	1–6.5 h	16 (16/0); 20–28 year; HV	Estimated blood Cmax: 74 ng/mL	Co, Db Pc, Rd	Cognitive/psychomotor performance	Y(cd)	Alc, B, P	U	[37]
Zopiclone; po; 7.5 mg	8.75–9.5 h (task); 10–11 h (driving)	18 (8/10); 55–75 year; HV	N	Co, Db Pc, Rd	Actual driving; Cognitive/psychomotor performance	Y/N	P	N	[61]
Zopiclone; po; 7.5 mg	10 h	30 (15/15); 21–45 year; HV	N	Co, Db Pc, Rd	Actual driving; Cognitive/psychomotor performance	Y/N	Alc, P	U	[102]

[a] Abbreviations for drug, dose, and administration: *d*-A = dexamphetamine, *d*-MA = dexmetphamphetamine, *d,l*-MA = *dextro,levo*-methamphetamine, MA = methamphetamine, MDMA = 3,4-methylenedioxymethamphetamine, MPH = methylphenidate, THC = tetrahydrocannabinol; HD = high dose, LD = low dose, MD = medium dose; im = intramuscular, inh = inhalation, inj = injection, IR = immediate release, iv = intravenous injection, po = per os (through the mouth), XR = extended-release.

[b] Abbreviations for subjects: f = number of female; HV = healthy volunteer; m = number of male; *n* = total number.

[c] Abbreviations for pharmacokinetics: Cmax = maximum concentration, h = hours; min = minutes.

[d] Abbreviations for methodology: Bl = blinded; Co = crossover; Db = double blind; Pc = placebo controlled; Rd = randomized.

[e] Abbreviation for effects: ↑ = improvement; cd = concentration dependent; dd = dose dependent; N = no impairment; Y = impairment.

[f] Abbreviation for control group: Alc = alcohol; B = baseline; P = placebo.

[g] Abbreviation for biological samples: B = blood; Br = breath (testing for alcohol); N = none; U = urine.

The included semi-experimental studies are presented in **Table 2**.

B. On-the-Road Driving

The on-road driving-test methodology was developed in The Netherlands [70] and resulted in a highly standardized test [103] that is performed on a public highway in normal traffic. The test driver operates a specially instrumented vehicle over a 100-km distance on a highway. Drivers are instructed to drive with a steady lateral position within the right traffic lane while maintaining a constant speed of 95 km/h. The speed and mean lateral position are continuously recorded, and the weaving of the car is calculated as the standard deviation of lateral position (SDLP), and in addition a broad range of driving tasks at operational and tactical levels may also be assessed [77], allowing all behavioral levels to be tested.

In a road-tracking test [77], instruments are continuously measuring the distance between the vehicle and the left lane-line. The data are used to calculate means and variances for speed and position, such as the standard deviation of lateral position (SDLP).

In a car-following test [77], two motor vehicles are driving in tandem with a distance of 15–30 m between the cars. The first vehicle is under an investigator's control, and the following vehicle is under the test driver's control. During the experiment, speed changes of the leading car are controlled by a computer, which also activates the brake lights at random. The test driver in the following car is instructed to react to brake lights by removing his/her foot from the speed pedal as quickly as possible. The speed, distance between cars, and reaction times are recorded.

C. Driving Simulator

In a driving simulator, the subjects perform a computer simulation of a driving task. Tests in a driving simulator are used to evaluate driving performance. However, even very sophisticated driving simulators cannot fully replicate real driving conditions [42].

The main advantages of driving simulation are that driving tasks can be standardized and data can be obtained safely.

The risk of simulator sickness may be a problem when using driving simulators [8]. This is a form of motion sickness in which participants experience slight cognitive disorientation or dizziness and often nausea. In some cases, this sickness can occur to a degree that participants cannot complete the driving course.

It is necessary to practice on the simulator situation, both to reduce dropout as a result of nausea and to ensure familiarization to the driving environment of the simulator.

Table 2. Semi-experimental studies

Substance group	Subjects (*n*)[a]	Methodology[b]	Conc.-dependent association (Y/N)	Reference group	Ref.
Amphetamine Methamphetamine	878	CTI	Y	None	[39]
Amphetamine	70	CTI	N	None	[48]
Benzodiazepines	818	CTI	Y	10,759 (alcohol only)	[17]
Benzodiazepines	818	CTI	Y	None	[19]
Codeine	43	CTI	Y	None	[5]
Flunitrazepam	415	CTI	Y	None	[18]
GHB	25	CTI	Y	32 (GHB negative)	[2]
Heroin	70	CTI	Y	79 (negative)	[4]
Methadone	635 (methadone) 10 (methadone only)	CTI	N	None	[11]
THC	589	CTI	Y	3,480 (alcohol only) 79 (negative) 894 (THC & alcohol)	[16]
THC	456	CTI	Y	None	[51]
Zolpidem Zopiclone	70 (zopiclone only) 43 (zolpidem only)	CTI	N	3,480 (alcohol only)	[36]

[a] Abbreviations for subjects: *n* = total number.
[b] Abbreviations for methodology: CTI = clinical test of impairment.

D. Psychomotor and Cognitive Testing

Driving is an example of complex behavior [105], where simultaneous use of multiple skills is required. Laboratory tests are used to measure specific driving-related skills [109]. They can be useful in examining functions that are essential to safe driving even though they can never fully reproduce the complexity of real driving [43]. Examples of performance tasks are reaction time, attention, divided attention, psychomotor skills, visual functions, tracking, and en-/decoding [55]. Some experimental studies also include physiological measurements, such as blood pressure, pulse and eye movements, as well as subjective evaluations, mainly using Visual Analogue Scales to report effects such as drug liking, sedation, or pain. The results of subjective evaluations have not been included in our review.

E. Studies of Clinical Signs of Impairment after *Ad Libitum* Intake (Semi-Experimental Studies)

In cases of suspected drugged driving, a CTI can be performed when collecting the blood sample from the apprehended driver. The observations retrieved from the CTI can be evaluated in relation to the drug findings. This type of study does not obtain objective information regarding time and the amount of drug intake. However, an individual evaluation of impairment can be made.

II. RESULTS

A. Benzodiazepines and Related Drugs

Benzodiazepines are classified as anxiolytic and hypnotic drugs and act selectively on $GABA_A$ receptors [80]. All benzodiazepines have common pharmacodynamic properties [27]. We have included 17 studies on acute effects of benzodiazepines that met our inclusion criteria in this review (*see* also Table 1).

Abanades et al. [1] found that 1.25 mg flunitrazepam impaired psychomotor performance (digit symbol substitution test, Maddox Wing, and balance task) up to 5 h after administration.

Bocca et al. [12] administered 1 mg flunitrazepam to subjects aged 55-65 years and found that driving parameters measured in a driving simulator were not affected by flunitrazepam. They also administered 10 mg zolpidem and 7.5 mg zopiclone to subjects at nighttime and tested simulated driving the next morning. The study showed that both drugs had residual effects on driving performance 10 h after the drugs were administered.

Bramness et al. [17] studied the relationship between drug concentrations in benzodiazepine users and performance in a CTI in persons suspected of driving under the influence. Only drivers found positive for one single drug were included in this study. The probability of being assessed as impaired rose with increasing blood levels of diazepam, oxazepam, and flunitrazepam.

Bramness et al. [19] studied the relationship between benzodiazepine concentration and simple CTI in apprehended drivers suspected of driving under the influence of benzodiazepines. Thirteen of 25 subtests and observations were significantly related to blood benzodiazepine concentrations.

Carter et al. [20] studied psychomotor and cognitive effects and found that triazolam (0.2 and 0.4 mg/kg) impaired all tests examined. Triazolam also produced an underestimation of cognitive impairment as measured with subjective ratings of the drug effects.

Ferrara et al. [30] found that lorazepam (approximately 2 mg) worsened performance on all psychomotor tests (critical fusion frequency, critical tracking test, response competition task, choice reaction time, and visual vigilance task) as compared to placebo.

Gustavsen et al. [38] studied psychomotor effects at three levels of behavior (i.e., automative behavior, control behavior, and executive planning behavior) and found that 10 mg zopiclone caused impairment at all levels 1 h after intake. Blood zopiclone concentrations at approximately 39 ng/mL, achieved 1 h after intake of 10 mg zopiclone, were accompanied by comparable or more impairment than blood alcohol concentration (BAC) of 0.74 g/L. No test components were impaired at 6.5 h after administration, in spite of the fact that the same concentration in blood was associated with impairment about 1 h after intake. The group also found a clear positive concentration-effect relationship above 16 ng/mL (up to 74 ng/mL) for zopiclone (5 and 10 mg) for both automotive and control behaviors as well as a modest relationship for executive planning behavior [37].

Gustavsen et al. [36] investigated the relationship between zopiclone and zolpidem blood concentrations and driving impairment as judged by a CTI. No significant relationship was found, although there was a tendency toward an increased proportion of drivers judged as impaired with higher blood zopiclone concentrations. For alcohol-positive drivers, the proportion of impaired drivers was significantly related to blood BACs.

Leufkens et al. [62] found that the acute impairing effects of 1 mg alprazolam extended-release (XR) on driving and psychomotor functions were generally less, as compared to its 1 mg immediate-release (IR) equivalent, but still of sufficient magnitude to increase the risk of impairment. Both formulations impaired driving performance severely between 4 and 5 h after administration. The magnitude of driving impairment with XR formulation was about half of that observed with IR.

Leufkens and Vermeeren [61] found that 7.5 mg of zopiclone impaired a highway driving test as well as cognitive and psychomotor tests in healthy elderly subjects aged 55–75 years at least until 11 h after intake. The magnitude of impairing effects was comparable with those found previously in younger volunteers. They also concluded that 20 mg temazepam was unlikely to impair driving 10 h or more after bedtime administration in healthy elderly subjects.

Mattila et al. [67] studied the effects of 15 mg diazepam, 30 mg oxazepam, 15 mg zolpidem, and 7.5 mg zopiclone on performance (symbol digit substitution, simulated driving, flicker fusion, and body sway) and memory. The data indicate that zolpidem produces more decrements on psychomotor performance and immediate memory and learning than the comparator drugs. All drugs impaired three or more out of the five psychomotor tests performed.

Vanakoski et al. [99] tested driving after intake of diazepam in subjects aged 22–24 years (15 mg) and 55–77 years (10 mg), under light and dark conditions, and found that simulated driving was impaired in both groups compared to baseline and placebo. It was concluded that young subjects achieved good baselines scores but were sensitive to diazepam and alcohol, whereas older subjects showed poorer baseline scores but were less sensitive to both drugs.

Vermeeren et al. [102] studied effects of 7.5 mg zopiclone on actual driving, and concluded that zopiclone caused marked residual impairment 10 h after intake and that patients should be advised to avoid driving the morning after zopiclone administration. The subjects did not feel significantly less alert in the morning after zopiclone than after placebo. The magnitude of impairment in the driving test (SDLP) after zopiclone was twice that observed after alcohol with an average BAC of 0.3 g/L.

Verster et al. [107] found a dose-response relationship between 10 and 20 mg of zolpidem as well as an impaired performance of actual driving, memory, and psychomotor performance after 20 mg zolpidem. Driving ability was measured 4 h after administration and memory and psychomotor performance (word learning test, critical tracking test, divided attention test, digit substitution test) 6 h after administration. Relative to placebo, SDLP after both doses of zolpidem were of a greater magnitude than SDLP observed at BACs up to 0.5 g/L. On the other hand, the SDLP after the recommended dose of zolpidem (10 mg) was comparable to SDLP observed in placebo conditions in previous investigations.

Verster et al. [108] administered 1 mg alprazolam to healthy volunteers and test subjects who then performed a standardized driving test as well as a laboratory test battery. Alprazolam caused serious driving impairment and significantly impaired performance on the laboratory tests compared to placebo. The increment of SDLP caused by alprazolam was comparable to a BAC of 1.5 g/L as shown in a previous study [65].

Zacny et al. [113] tested psychomotor and cognitive performance in healthy volunteers after 2 mg lorazepam, and found significant impairment on all tests performed.

B. Cannabis

The most commonly used cannabis products are marijuana and hashish, both derived from the plant *Cannabis sativa* [46]. The main psychoactive compound is Δ^9-tetrahydrocannabinol (THC). We have included nine studies on acute effects of cannabis that met the inclusion criteria in this review (*see* also Table 1).

A driving simulator study, performed by Downey et al. [25], illustrated how THC negatively affects driving ability in both regular and nonregular THC users after administration of cannabis cigarettes containing 1.8% THC (0.8 g cigarette) and 3% THC (1.8 g cigarette), which represents about 14 mg and 53 mg THC, respectively [71]. Generally, experienced cannabis users displayed more driving errors than nonregular cannabis users. The mean level of THC in plasma before driving was higher in the regular cannabis users (approximately 100 ng/mL) than nonregular users (approximately 80 ng/mL). Driving was tested 25 min after smoking cannabis. The mean THC blood concentrations after low and high dose were 73 and 90 ng/mL, respectively, before driving and 38 and 45 ng/mL, respectively, after driving.

Dumont et al. [29] found that THC (4+6+6 mg) induced cognitive impairment but did not affect eye movements compared to placebo.

Khiabani et al. [51] studied the relationship between THC concentration in blood and impairment in apprehended drivers suspected of driving under the influence of drugs. The time between apprehension and completing the CTI with simultaneous collection of blood samples was about 2 h. Drivers with blood THC concentrations above 3 ng/mL had an increased risk for being judged impaired by CTI compared to drivers with lower concentration ranges. The relationship between concentration and impairment at the time of CTI and blood sampling does not necessarily reflect the degree of impairment at the time of driving.

Lenné et al. [60] tested simulated driving performance in experienced and inexperienced drivers and found dose-related impairment. Cannabis was associated with increases in speed and lateral position variability; a high dose of THC was associated with decreased mean speed, increased mean and greater variability in headways (distance between cars in car-following task), and longer reaction time.

Actual driving performance was tested by Ramaekers et al. [78] after administration of two doses of THC (100

and 200 µg/kg, i.e. about 7 mg and 14 mg). Both doses of THC significantly impaired the subjects' performances in the driving tests, and both doses increased SDLP more than a BAC of approximately 0.4 g/L.

Ramaekers et al. [79] measured perceptual motor control, dual task processing, motor inhibition, and cognition in heavy cannabis users, and found that THC (400 µg/kg, i.e. about 28 mg) generally did not affect task performance. THC did not affect performance of the critical tracking task, the stop-signal task and the Tower of London test, tasks that have previously been shown to be very sensitive to the impairing effects of THC when administered to infrequent cannabis users. It was concluded that heavy cannabis users develop tolerance to the impairing effects of THC on neurocognitive task performance, but no cross-tolerance to the impairing effects of alcohol.

A moderate dose of alcohol (BAC 0.5 g/L) and a THC dose of 13 mg were equally detrimental to some of the driving abilities (reaction time and steering wheel variability), with some differences between the drugs, as measured in simulated driving by Ronen et al. [83]. After THC administration, subjects drove significantly slower than in the control condition, whereas alcohol caused subjects to drive significantly faster. The effects on driving ability were dose-dependent at dosages of 13 and 17 mg THC. No THC-related effects were measured 24 h after smoking the high dose of THC.

Ronen et al. [82] studied the effect of THC (13 mg, smoked) on performance of simulated driving and nondriving tasks (e.g., reaction time) and found that THC impaired both driving and nondriving performance.

Van Wel et al. [98] demonstrated that heavy cannabis users showed impairment in a broad range of neuropsychological domains during THC intoxication. The tests used measured impulse control and psychomotor function (critical tracking test, divided attention test, matching familiar figures test, stop signal test, and Tower of London test). Single doses of cannabis (300 µg/kg, i.e., about 21 mg, smoked) impaired psychomotor performance and increased response errors during impulsivity tasks.

C. Opioids

The term opioid refers to substances with morphine-like effects [80]. Opioids, acting through the µ-opioid receptor, are widely used as analgesics. The opioid drug class includes numerous compounds that are structurally related to morphine and many other compounds that are pharmacologically related, but structurally unrelated [95]. The drugs included in our review were buprenorphine, codeine, fentanyl, methadone, morphine, and oxycodone. Nine studies on acute effects of opioids met the inclusion criteria (*see* also Table 1).

Amato et al. [3] tested driving performance in healthy volunteers using a driving simulator and found that driving and psychomotor performance were not affected by any of three codeine doses administered (20, 40, and 60 mg).

Bachs et al. [5] studied the relationship between codeine blood concentration and the conclusions from the corresponding individual CTI in apprehended drivers suspected of drugged driving. Only cases with detected codeine but not morphine were included. The odds ratios (ORs) for being judged as impaired were 6 and 19 for the "medium high" and "high" codeine blood concentration group, respectively. Codeine appeared to have some concentration-dependent effect on the central nervous system, independent of measurable morphine blood concentration, supporting the view that some codeine effects are not mediated by its conversion to morphine.

Bachs et al. [4] found no relationship between the concentration of morphine, as the main metabolite of heroin, and the results from a CTI. However, concentration-dependent effects were observed for the pharmacologically active metabolite morphine-6-glucuronide (M6G) and the sum of morphine and M6G.

Bernard et al. [11] found no correlation between methadone blood concentration and impairment as judged by a CTI either when detected alone or in combination with other drugs.

Pickering et al. [73] found that 30 mg codeine caused a longer choice reaction time than did 37.5 mg tramadol in young healthy volunteers; none of the drugs affected a memorization test and no difference was seen between the two treatments.

Schneider et al. [85] administered 0.2 µg/kg fentanyl by injection to healthy volunteers and compared the results of the cognitive testing to placebo and BAC 0.3 g/L. In contrast to the alcohol data, fentanyl (as compared to placebo) produced a significant impairment of auditory reaction time, signal detection, sustained attention, and a subtest of the memory test. The fentanyl plasma concentrations measured in relation to the testing were comparable to patient plasma levels when fentanyl is used as an analgesic during anesthesia in outpatient surgical procedures.

Verster et al. [104] found no significant treatment effects of oxycodone (5 and 10 mg) on driving ability relative to placebo, although a significant dose-response effect was found for SDLP. The increment of SDLP was, however, found to be less than that observed with BAC of 0.5 g/L.

Zacny et al. [113] tested psychomotor and cognitive performance in healthy volunteers after 10, 20, and 30 mg of oral oxycodone, and found impairment in some of the tests after the higher doses, indicating that psychomotor impairment may occur with clinically prescribed doses of oxycodone.

Zacny et al. [114] found no evidence of impairment of psychomotor and cognitive performance after 10 mg of oral oxycodone compared to placebo.

D. Stimulants

Among the drugs with stimulating CNS effects are amphetamine, methamphetamine, MDMA, cocaine, and methylphenidate. These drugs are widely used as recreational drugs and sometimes for therapeutic purposes. We have included 19 studies on the acute effects of stimulants that met the inclusion criteria in this review (*see* also Table 1).

Bosker et al. [14] tested three acute doses of MDMA (25, 50, and 100 mg) in recreational MDMA users. In general, MDMA did not affect any of the driving measures of actual driving; neither did it change the impairing effects due to sleep loss.

Dumont et al. [28] found an increase in psychomotor speed, but not accuracy, after administration of 100 mg MDMA. In another study, Dumont et al. [29] found that saccadic eye movements (a measure for psychomotor speed and sedation), immediate recall, and body sway were impaired after administration of single acute doses of 100 mg MDMA in regular users of ecstasy.

Gustavsen et al. [39] found a positive concentration–effect relationship between blood concentrations of amphetamine and/or methamphetamine and clinical impairment as assessed by CTI in drivers suspected of driving under the influence of non-alcoholic drugs. The relationship reached a ceiling at blood amphetamines concentrations of 270–530 ng/mL. The concentration–effect relationship was apparently less pronounced than previously found in studies regarding benzodiazepines, carisoprodol, codeine, and alcohol. Younger drivers were more often judged impaired than older drivers at similar concentrations.

Hjälmdal et al. [45] studied simulated driving performance and found few significant results, showing both improved and worsened driving performance, after administering 10 or 40 mg of d-amphetamine to healthy volunteers. The low dose led to improved driving performance for three out of the five primary indicators measured. The positive effects of the low dose were not further improved or even sustained by increasing the dose, which might indicate that at still higher doses there are few or no positive effects of *d*-amphetamine. The data did not show any evidence that taking *d*-amphetamine prevented the subjects from becoming successively sleepier during the night, suggesting that the drug does not compensate for impairment of driving due to fatigue.

Jones [48] did not find any correlation between blood amphetamine concentration and results of clinical tests of impairment in apprehended drivers.

Kirkpatrick et al. [54] administered 20 and 40 mg methamphetamine and found that performance on tasks measuring response time and vigilance were improved by the 40 mg methamphetamine dose. They also found that 100 mg MDMA had no effect on performance.

Kirkpatrick et al. [53] found in another study that 10 mg methamphetamine did not have acute nor residual cognitive or psychomotor effects.

Kuypers et al. [57] found that MDMA (75 and 100 mg) reduced SDLP and standard deviation of speed in actual driving.

Ramaekers et al. [77] tested actual driving and concluded that 75 mg MDMA may improve performance in certain aspects of the driving task, such as road-tracking performance (SDLP), but cause impairment in other aspects, such as accuracy and speed adaption during car-following performance. In the same study it was found that 20 mg methylphenidate improved tracking performance as indicated by a significant decrease in SDLP.

Silber et al. have studied simulated driving performance following amphetamine or methamphetamine administration in several studies [87–90]. The studies provide evidence of low-level amphetamine-related enhancement of function [89], but no significant (overall) effect on simulated driving performance [87,88] and a decrease in overall simulated driving ability following amphetamine administration [90] at the same dosages (0.42 mg/kg). The authors concluded that the results shed little light as to how amphetamine may contribute to driving fatalities as there were no direct demonstrations of amphetamine-related impairments [89]. It is worth mentioning that the studies performed by Silber et al. are all describing the acute effects of amphetamine and methamphetamine after intake of single and relatively low (therapeutic) doses, in contrast to a realistic setting with binge or intensive use and higher doses.

Another simulated driving study, performed by Simons et al. [92], showed that 10 mg dexamphetamine alone caused the least number of collisions and less passing of red traffic lights, and the best performance on divided attention and vigilance tasks, as compared to alcohol (BAC 0.64–0.91 g/L) or a combination of the two substances.

A simulator study by Stough et al. [93] showed that overall impairment scores for driving and signaling were worse in the methamphetamine condition (0.42 mg/kg) compared to placebo, but this difference was not significant. They also found that the overall impairment scores for driving and signaling were worse in the MDMA condition compared to both the placebo and methamphetamine conditions.

Stough et al. [94] found more accurate performance on a choice reaction task in the methamphetamine condition (0.42 mg/kg) compared to placebo, whereas impairment of working memory was observed. They also found poorer performance in the MDMA condition at peak concentration for the trail-making measures, and a trend level of working memory, as compared to the placebo condition.

Van Wel et al. [98] found that single doses of cocaine improved psychomotor function and decreased response time in impulsivity tasks, but increased errors, in heavy cannabis users.

Veldstra et al. [101] tested driving performance and traffic safety by means of a driving simulator after administration of 100 mg MDMA. The study showed that simulated driving, including SDLP, improved under the MDMA condition compared to both placebo and alcohol.

E. GHB

GHB is a potent sedative and anxiolytic drug with additional euphoric effects. In addition to being prescribed to patients with narcolepsy and its previous use as an anesthetic, GHB is a popular recreational drug of abuse [26,69]. It has a substantial risk of acute toxicity after overdose [32,52]. Drivers apprehended by the police for suspicion of DUI testing positive for GHB show signs of sedation as well as agitation, impaired balance, nystagmus, and irrational behavior [2,15,50]. We have included four studies on acute effects of GHB that met the inclusion criteria in this review (*see* also Table 1).

Abanades et al. [1] tested a psychomotor performance battery. Two different doses of GHB were administered (40 and 60 mg/kg), and the negative effects of GHB were dose-dependent and peaked 1 h after its administration.

Al-Samarraie et al. [2] investigated the possible relationship between GHB blood concentrations and clinical effects in car drivers. During an 8-year period 25 car drivers who had tested positive for only GHB in their blood were identified among drivers suspected of drugged driving. The median blood GHB concentration was 131 μg/mL, which is quite high, and CTI results indicated impairment that depressed central nervous system activity. The effect of GHB on the degree of impairment and consciousness tended to be concentration-dependent and the number of drivers who were impaired or had reduced consciousness was highly increased in GHB-drivers compared to controls.

Ferrara et al. [30] administered two therapeutic doses of GHB (12.5 and 25 mg/kg) and found that performance after both doses was not different from placebo. Psychomotor performance was measured using tests of attention, vigilance, alertness, short-term memory, and psychomotor coordination.

Johnson and Griffiths [47] reported that GHB (1-10 g/70 kg) caused significant decreases in performance on all cognitive and motor tasks tested, with peak effects at 60 min. Dose-related effects were observed.

F. Ketamine

Ketamine is used therapeutically to induce anesthesia prior to the administration of a general anesthetic or for brief surgical procedures [20]. Ketamine is also used recreationally for its mood-altering properties. The misuse of ketamine as a recreational drug has increased remarkably over the last decade [33]. We have included two studies on acute effects of ketamine in this review that met the inclusion criteria (*see* also Table 1).

Carter et al. [20] found that 0.2 mg and 0.4 mg ketamine administered intramuscular impaired several of the psychomotor and cognitive tasks measured (i.e., balance, circular lights, digit symbol substitution task, divided attention task, and episodic and working memory), and the results suggests that the impairing effects of ketamine are more closely related to its dissociative effects as opposed to its sedative effects.

Krystal et al. [56] assessed a spectrum of behaviors associated with frontal cortex functionality (e.g., vigilance to visual stimuli, distractibility, verbal fluency, abstraction, and the Wisconsin Card Sorting Test) as well as memory and psychomotor function after administration of a bolus of 0.26 mg/kg followed by a 1-h infusion of 0.65 mg/kg ketamine. Ketamine impaired six out of seven functions measured; one of the tests also showed dose-dependent impairment.

G. Antihistamines and Antidepressants

We did not find any studies that complied with our inclusion criteria.

III. DISCUSSION

A large number of experimental studies have been performed. We have made literature searches with rather limiting inclusion criteria; therefore, a number of studies that did not comply with our criteria have not been taken into consideration in this review. Making limitations based on a judgment of quality in the way we have done in this review makes it easier to select the most relevant studies, but also implies a risk of leaving out studies of importance.

Publication bias is a well-known problem with regard to experimental studies. Researchers and journals might not want to publish null results; consequently, it is more likely that positive findings are published. This would further influence the results of systematic literature reviews and meta-analysis.

Only publications in English have been included. Relevant studies might have been lost due to this limitation. Experimental studies published before 1998 were also not included in the present article since they have been discussed in an earlier review article on publications published before 1998 [68].

A. Benzodiazepines and Related Drugs

1. Impairing Effect of a Single Dose

All of the studies on acute effects, except one, found that the different benzodiazepines and benzodiazepine-like drugs cause some degree of impairment [1,12,20,30,37,38, 61,62,67,99,102,107,108,113]. Only one study on acute effects reported that a benzodiazepine (flunitrazepam, 1 mg) did not cause impairment, as assessed by a driving simulator test performed 10 h after drug administration [12]. The explanation for this could be that the dose administered was not sufficient to impair performance at the time of testing. Also previous reviews [22,27,105,109] and meta-analysis [84] have concluded that benzodiazepines can impair skills relevant to safe driving. In general, these papers reported that therapeutic doses of long-acting benzodiazepines, such as diazepam and flunitrazepam, can impair skills relevant to safe driving, whereas shorter-acting benzodiazepines, such as oxazepam, show little or no significant adverse effects on psychomotor performance. Benzodiazepine-like drugs such as zopiclone, zolpidem, and zaleplon, can also cause significant effects on driving. The duration of action of benzodiazepines is largely dependent on their pharmacokinetic half-lives. Data demonstrating impairing effects on driving-related skills will therefore depend critically on the time of testing in relation to time of administration [27].

2. Dose/Blood Concentration Effect Relationship

A positive concentration-effect relationship was found for zopiclone with respect to automotive and control behaviors [37].

Semi-experimental studies demonstrated a concentration-effect relationship for benzodiazepines among persons suspected of drugged driving [17,19], but no such effect was found for zopiclone and zolpidem [36].

Dose-dependent performance impairment has been described for hypnotics [105]. In a meta-analysis the concentrations of several benzodiazepines that produced impairment equivalent to a BAC of 0.5 g/L has been determined [10]. Berghaus et al. performed, as part of the European DRUID project, a meta-analysis of studies measuring acute effects after intake of several benzodiazepines as well as z-hypnotics. For example, experimental studies with single administration of diazepam in doses between 5 mg and 40 mg to healthy volunteers were included. Curves showing time- and concentration-dependent impairment were calculated. It was established that a BAC of 0.5 g/L caused impairment in 30% of the tests, and the same percentage of impaired tests was seen at a diazepam concentration of 320 ng/mL in plasma (i.e., about 179 ng/mL blood). A dose-/concentration–effect relationship was found for diazepam. The equivalents to a BAC of 0.5 g/L for the other benzodiazepines and z-hypnotics were, in plasma (blood), as follows: alprazolam 9 (7.3) ng/mL, checked doses 0.25–2.0 mg; flunitrazepam 5.4 (4) ng/mL, checked doses 0.5–4.0 mg; lorazepam 9 ng/mL, checked doses 0.5–9.0 mg; nitrazepam not calculable due to different impairment profiles dependent on time of administration; oxazepam 330 (300) ng/mL, checked doses 10–90 mg; triazolam 1.6 (1) ng/mL, checked doses 0.125–3.0 mg; zopiclone 26 (23) ng/mL, checked doses 2.5–10 mg; zolpidem 71 (50) ng/mL, checked doses 5–20 mg. Furthermore, an expert panel [110] proposed concentrations for several benzodiazepines in blood that were equivalent to a BAC of 0.5 g/L with respect to psychomotor impairment: alprazolam 6 ng/mL; diazepam 143 ng/mL; flunitrazepam 3 ng/mL; nitrazepam 42 ng/mL; oxazepam 430 ng/mL; zolpidem 77 ng/mL, and zopiclone 23 ng/mL.

3. Tolerance

Acute tolerance to the effects of zopiclone was demonstrated as blood concentrations measured less than 1 h after intake were more often accompanied by impairment than the same blood drug concentration at a later point of time [38].

It has been postulated that the phenomenon of acute tolerance can be predicted at a population level, but not for individuals [24]. Previous studies have shown that regular users will develop tolerance to most of the adverse effects of benzodiazepines [27]. A meta-analysis concluded that moderate-to-large weighted effect sizes were found for all cognitive domains suggesting that long-term benzodiazepine users were significantly impaired in all of the areas that were assessed as compared to controls [6]. Results of meta-analyses also indicated that long-term benzodiazepine users showed recovery of function in many areas after withdrawal, although there may have been some permanent deficits or deficits that took longer than six months to completely recover [7]. It has been described that impairment was most pronounced after treatment initiation, typically after one or two nights of administration [105].

4. Interaction with Alcohol

None of the studies included in this review evaluated interaction with alcohol.

In general an increased impairment of psychomotor and other driving skills has been observed when alcohol

was administered to subjects who already had consumed benzodiazepines, especially during the first days to weeks of treatment with these drugs [27]. It has been described that the combination of alcohol and temazepam, lorazepam, or triazolam caused clear impairment [109].

5. Comparison with findings in epidemiological studies

Most epidemiological studies found an association between the use of benzodiazepines or z-hypnotics and increased crash risk [34]. The reviewed experimental studies are on line with the epidemiological studies indicating that a significant risk of road traffic crash (RTC) involvement is present among users of benzodiazepines/z-hypnotics.

B. Cannabis

1. Impairing Effect of a Single Dose

Most of the studies included in this review found that cannabis affected driving ability in regular [25,60,78,82, 83,98] and nonregular [25,60] users. All of these studies, but one [98], investigated the effects of THC on actual driving or simulated driving. Dumont et al. [29] found that THC induced cognitive impairment but had no significant effect on eye movements. Ramaekers et al. [79] found that a high dose of THC of about 28 mg generally did not affect performance tests (i.e., the critical tracking test, the stop-signal task, and the Tower of London test) in heavy cannabis users. The divided attention task was, however, affected by THC, indicating that the sensitivity to different tests can vary.

It has been stated that results from experimental studies clearly indicated that cannabis use can have a detrimental impact on driving ability, as it impaired some cognitive and psychomotor skills that are necessary for driving [109]. A review of experimental studies concluded that performance of complex tasks deteriorates after smoking cannabis [41]. Another review concluded that there was strong evidence from performance studies that THC had significant effects on the cognitive and psychomotor tasks associated with driving, but that it could still be debated whether these effects increased RTC risk [46].

2. Dose/Blood Concentration Effect Relationship

Dose-related impairment was observed in both inexperienced [60] and experienced drivers [60,78,83], as tested in simulated driving [60,83] and actual driving [78].

Semi-experimental studies revealed a positive relationship between the blood THC concentration and the number of persons classified as impaired by a CTI [16,51]. Similarly, Papafotiu et al. [71] found a positive correlation between the dose of THC administered and the impairment found when using Standardized Field Sobriety Tests. It is worth mentioning that a time lag between intake of cannabis and blood sampling would not obscure the relationship between blood THC concentration and clinical outcome as long as the blood sample is collected at the same time as CTI is performed.

The National Highway Traffic Safety Administration (NHTSA) expert panel [22] assessed the driving risks after use of cannabis, and stated that the use of low doses caused moderate impairment, whereas severe impairment was seen after high doses and chronic use. Previously, it has been found that blood concentrations of THC were not closely related to the degree of impairment [81]. An international working group of experts evaluated possible approaches to developing per se limits for driving under the influence of cannabis [35] and concluded that epidemiological studies indicated that serum concentrations of THC below 10 ng/mL (i.e., about 5 ng/mL blood) were not associated with an elevated RTC risk, and experimental studies on driving-related skills suggested that a THC concentration of 7–10 ng/mL in serum (i.e., about 3.5–5 ng/mL blood) was associated with impairment equivalent to a BAC of 0.5 g/L. A meta-analysis calculated that a 0.5 g/L alcohol equivalent was around 3.8 ng/mL THC in plasma (i.e., about 2 ng/mL blood) with respect to impairment, but it was stated that there was a considerable variation [10]. An expert panel proposed that a THC concentration in blood of 3.0 ng/mL is equivalent to a BAC of 0.5 g/L with respect to impairment [110].

3. Tolerance

A study on neurocognitive task performance generally demonstrated that heavy cannabis users developed tolerance to the impairing effects of THC, but not cross-tolerance to the impairing effects of alcohol [79]. The study describes that tolerance was not apparent in all performance tasks, which could explain that some studies, on the other hand, have reported that heavy users showed impaired psychomotor performance [98], and experienced cannabis users made more driving errors than nonregular users [25]. It has also been suggested that drivers might be able to compensate for the effects of cannabis by, for example, driving at slower speeds [60].

Neurocognitive performance has been tested in occasional and heavy users, and it was observed that THC affected performance in more tasks in occasional users than in heavy users [76]. Cannabis smoking impaired psychomotor function significantly more in occasional users than in frequent users [23].

4. Interaction with Alcohol

Some studies found that the combination of THC and alcohol produced synergistic effects [25,78,82], whereas one study found that alcohol did not produce synergistic

effects when combined with cannabis [60]. The latter study also described that alcohol alone, at the doses used (0.4 and 0.6 g/kg), had few effects on simulated driving, indicating rather low sensitivity of the test, at least to the acute effects of alcohol, which could explain the lack of synergistic effects. Additive and synergistic effects of alcohol and THC were shown in heavy cannabis users [79].

Additive effects of THC and alcohol on driving performance have been observed by others [58,81,86]. Additive effects were reported in occasional cannabis users [75]. Verstraete et al. [109] concluded that combining alcohol and marijuana would eliminate the ability that marijuana users may have to effectively compensate for some impairing effects while driving by using different behavioral strategies. On the other hand, some studies found that the combination of cannabis and alcohol did not produce different effects on performance than when each drug was tested individually [58,63].

It has been shown that co-administration of alcohol and cannabis gave significantly increased blood THC concentrations compared to cannabis alone [25,40]. This might explain increased performance impairment observed from cannabis-alcohol combinations.

5. Comparison with Findings in Epidemiological Studies

Epidemiological studies have reported a significant association between cannabis use and RTCs and injuries [34]. Cohort, case-control, and responsibility/case-crossover studies have found a significant association, but some studies also report lack of such association. The reviewed experimental studies are on line with the epidemiological studies indicating that there is an increased risk of RTC in both experienced and inexperienced users of cannabis.

C. Opioids

1. Impairing Effect of a Single Dose

The studies included in this review found variable results for opioids with respect to impairment. The reason for this could be the sensitivity of the different tests used and/or the sensitivity of the participants to drug-induced effects. Pickering et al. [73] found that 30 mg codeine affected choice reaction time, and Amato et al. [3] found that 20 mg codeine impaired SDS (standard deviation of speed) but did not find any effect on SDLP or reaction time after administration of up to 60 mg. Also for oxycodone, some studies found that some tests were affected while others were not [104,113], and one study found no effect at all after 10 mg [114]. Schneider et al. [85] found significant effects for fentanyl at a dose of 0.2 μg/kg.

The NHTSA expert panel [22] concluded that morphine can severely impair driving skills if used in acute situations or taken illicitly. A review of the literature on acute effects after administration of single doses of morphine to healthy, opioid-naïve subjects concluded that blood morphine concentrations below 14.3 ng/mL were probably accompanied by few effects in traffic-relevant performance tasks [97]. Verstraete et al. [109] summarized the acute effects of morphine, fentanyl, methadone, buprenorphine, and codeine as investigated in experimental studies, and concluded that opioids may cause some cognitive and psychomotor impairment. These effects are highly dependent on the type of opioid at issue and the dose administered, and are mostly moderate. Stout and Farrell [95] summarized the literature relating selected opioids to performance, specifically driving. They concluded that opioids appeared to impair psychomotor functioning in such a way that it is likely to be important for the performance of complex, divided-attention tasks such as driving, and that the impairment was notably more prevalent in individuals with no history of opioid use than individuals with long-term use. A systematic review [96] found that both methadone and buprenorphine were confirmed as having impairing potentials of cognitive and psychomotor functions in opioid-naïve subjects but not in compliant stable users with tolerance.

2. Dose/Blood Concentration Effect Relationship

A dose-response study of codeine found no correlation between concentration and effects [3]. Dose-dependent effect was observed for SDLP after administration of oxycodone [104].

A semi-experimental study found that codeine appeared to have some dose-dependent effect on the central nervous system in drivers suspected of drugged driving [5]. No correlation was found between methadone blood concentration and impairment as judged by the CTI, neither when detected alone nor in combination with other drugs [11]. Concentration-dependent effects for the combination of the heroin metabolites morphine and morphine-6-glucuronide in blood [4] in semi-experimental studies have been observed.

3. Tolerance

None of the studies included in this review evaluated tolerance.

A structured evidence-based review has included studies on psychomotor abilities, cognitive function, effect of opioid dosing on psychomotor abilities, motor vehicle driving violations and RTCs, and driving impairment as measured in driving simulators and off/on-road driving [31]. The majority of the reviewed studies appeared to indicate that opioids do not impair driving-related skills in opioid-dependent/tolerant patients. However, impairments of psychomotor and cognitive functions have been observed among both methadone-maintained

patients and buprenorphine-maintained patients when compared to control groups [96], and a systematic review concluded that it cannot be generalized that patients on stable opioid doses are safe to drive [66]. Studies have found that tolerance develops early to the duration and intensity of euphoria after use of morphine [22].

4. Interaction with Alcohol

Oxycodone (10 mg, oral) combined with alcohol (0.3 and 0.6 g/kg) did not affect psychomotor and cognitive performance [114], possibly due to insensitivity to the tests used or dosages being unable to produce impairment. It was observed that oxycodone decreased the absorption of alcohol [114]. No synergistic effects between alcohol and methadone or buprenorphine as used by maintenance participants were observed in a study of simulated driving [59].

5. Comparison with Findings in Epidemiological Studies

Most epidemiological studies also found statistically significant associations between use of opioids and RTC [34]. The reviewed experimental studies, on the other hand, indicate that opioids cause only moderate effects on driving-related performance.

D. Stimulants

1. Impairing Effect of a Single Dose

Most experimental studies of amphetamine, methamphetamine, and MDMA in doses of up to 40 mg amphetamine, 40 mg methamphetamine, and 100 mg MDMA found no major detrimental effect on psychomotor tests or actual driving [14,53,54,87,88]; some studies found minor improvements [28,45,54,57,77,89,92,94, 98,101], and some studies found some negative effects [29,45,77,90,93,94,98].

As part of the European DRUID project, a meta-analysis of studies measuring effects after intake of amphetamine and cocaine, and a review of results from studies on MDMA, was performed [10]. Doses up to 36 mg d-amphetamine were administered, and while some improvement was observed, none of the effects measured was impaired. The same results were found for the effects after cocaine administration in doses up to 210 mg. MDMA had primarily no risk potential on driver fitness, as tested with doses up to 125 mg of MDMA in experimental studies. Verstraete et al. [109] concluded that acute use of amphetamine and methamphetamine can have positive effects, as well as negative effects, on cognitive and psychomotor skills. Especially in sleep-deprived or fatigued subjects, stimulants can improve performance. Experimental studies of acute use of MDMA have also found both negative and positive effects on performance. A review of the effects of methamphetamine on human performance and behavior concluded that anything other than therapeutic administration of low-dose methamphetamine was likely to cause some impairment of performance in complex psychomotor tasks such as driving [64]. A PET scan study found that relatively high doses of amphetamine, presumably at least 1 mg/kg, increased cerebral glucose metabolism and caused signs of mania and thought disorder [111].

It can further be noted that amphetamine is administered in daily doses of 5–60 mg for therapeutic use in adults [9], in some cases probably somewhat higher, and doses up to 1 mg/kg body weight has been given to voluntary participants in experimental studies [111]. However, commonly abused doses are reported to be 100–1,000 mg/day, and up to 5,000 mg/day in chronic binge use [22]. Controlled experimental studies of these high doses cannot be performed for ethical reasons, and therefore higher concentrations of amphetamines are not studied. Large doses of amphetamines may have harmful effects on self-perception, critical judgment, and risk taking, whereas when the stimulating effects are disappearing, followed by a period associated with fatigue, anxiety, and irritability [34]. The single, therapeutic doses administered in these experimental studies do also not reflect the realistic setting of binging or intensive use of amphetamines.

2. Dose/Blood Concentration–Effect Relationship

Experimental studies have not found any dose-effect relationship. This is probably related to the fact that the doses used in experimental studies are small compared to the doses used by problem amphetamine users [39].

Semi-experimental studies have reported divergent results. A positive concentration–effect relationship between blood amphetamines concentrations and clinical impairment as assessed by CTI in drivers suspected of driving under the influence of non-alcoholic drugs was found [39]. The relationship reached a ceiling at blood amphetamines concentrations of 270–530 ng/mL. On the other hand, no relationship was observed between blood amphetamine concentration and impairment in another study of apprehended drivers [48]. It was reported that doses of approximately 30 mg amphetamine or methamphetamine did not impair performance on the SFSTs [91]. It can be noted that an oral dose of approximately 30 mg amphetamine has been shown to lead to blood concentrations up to approximately 100 ng/mL [89]. Current methamphetamine users were more likely to speed and to weave from side to side, as measured by SDLP, when simulator performance was studied [13]. The main measures of risky driving were not associated with current methamphetamine, or its main metabolite amphetamine, levels in blood.

The NHTSA expert panel [22] described that lower doses of amphetamines could cause improvement of some psychomotor tasks and otherwise had few effects on cognitive functioning, whereas at higher doses risk-taking increased and responses became inappropriate.

3. Tolerance

The development of tolerance was not investigated in the studies included in this review.

It has been stated that tolerance to the effects of amphetamines may develop [22,109]. Habituation to certain effects can occur within an intake (acute tolerance) so that the sense of intoxication decreases while the substance is still present in the body [64]. Significant subjective effects have been observed after administering methamphetamine, effects that subsided rapidly and before the concentrations in blood decreased markedly, suggesting development of acute tolerance [21]. A case series of drivers apprehended for driving under the influence of drugs reported abnormally high concentrations of amphetamine in blood, ranging from 5,000 ng/mL to 17,000 ng/mL [49]. The authors speculated that these very high concentrations were tolerated without any fatalities due to a pronounced adaption to the pharmacological effects of this drug.

Chronic tolerance to Ecstasy/MDMA in humans has been observed, and many recreational users reported reduced subjective efficacy with repeated drug use, together with dosage escalation, and bingeing [72].

4. Interaction with Alcohol

It was stated that oral methamphetamine combined with alcohol produced a profile of effects that was different from either drug alone [53]. Methamphetamine attenuated alcohol-related performance decrements as participants performed worse on measures of divided attention and vigilance following administration of alcohol alone. The combination of dexamphetamine and alcohol was associated with a higher frequency of red-light running and collisions than the dexamphetamine or placebo conditions in simulated driving [92]. The risk scenarios and measures employed in the study were very sensitive to both alcohol and the combination treatment. The impairing effects of alcohol on skills related to driving were not improved by the stimulatory effects of co-administration of 10 mg dexamphetamine.

A driving study found that MDMA moderated alcohol-induced impairment of road tracking performance (SDLP), but did not affect alcohol impairments of car-following and laboratory task performance [57], whereas another study did not find a significant effect on driving performance (e.g., SDLP) when combining the two drugs [101]. Equivalence testing in the latter showed that combined use may lead to impaired driving for some, but not all, drivers. Co-administration of MDMA and alcohol improved psychomotor speed, but impaired psychomotor accuracy, compared with placebo, and also reversed alcohol-induced sedation [28].

The combination of MDMA and alcohol has been shown to cause subjects to feel euphoric and less sedated and might have the feeling of doing better, but actual performance ability continued to be impaired by the effect of alcohol [44].

Plasma concentrations of MDMA have shown a 13% increase after the use of alcohol, whereas plasma concentrations of alcohol have shown a 9–15% decrease after MDMA administration [44].

5. Comparison with Findings in Epidemiological Studies

Epidemiological studies reported a clear association between use of amphetamines and cocaine and increased RTC risk [34]. After alcohol, amphetamines were found to be the substances associated with the highest RTC risk. It is likely that problematic amphetamine users and addicts constitute a larger traffic safety problem than drivers that occasionally are taking small doses of amphetamines to stay awake and alert during long journeys. The general lack of findings in controlled experimental studies reviewed in the present paper is not at odds with epidemiological findings that the use of amphetamines and cocaine, at least in higher doses, is associated with a significant RTC risk.

E. GHB

Abanades et al. [1] and Johnson and Griffiths [47] found dose-dependent effects of GHB on cognitive and psychomotor performance, whereas Ferrara et al. [30], who administered markedly lower doses of GHB than did the other two studies, found that psychomotor performance did not differ from placebo. On the other hand, Ferrara et al. tested performance in healthy volunteers, whereas Abanades et al. and Johnson and Griffiths tested subjects who were recreational users of GHB or had a history of sedative abuse, respectively.

A semi-experimental study found that the effect of GHB on the degree of impairment and consciousness tended to be concentration-dependent and the number of drivers who were impaired or had reduced consciousness was highly increased in GHB-drivers compared to controls [2].

The NHTSA expert panel [22] concluded that recreational use of GHB has the potential to produce moderate to severe driving impairment due to its ability to induce sleep and unconsciousness. It was reported that tolerance can develop to GHB with chronic abuse although tolerance does not develop to all effects of GHB, like enhanced sleep. Cross-tolerance exists between GHB and alcohol. Dose-dependent cognitive and psychomotor

impairment after acute use of GHB in doses typically consumed by users has been described [109]. Furthermore, it was found that there were additive, but not synergetic, effects of GHB and alcohol on cognitive impairment.

F. Ketamine

Both studies included in this review found that ketamine impaired cognitive and psychomotor tasks related to driving [20,56]; one test showed dose-dependent impairment [56].

A systematic review on the effects of ketamine on psychomotor, cognitive, visual, and perceptual functions related to safe driving using wider inclusion criteria has been published [33]. The authors concluded that significant impairment in multiple functional domains essential to driving have been described and could reasonably warrant an increased risk of dangerous driving under the influence of ketamine.

The NHTSA expert panel [22] concluded that ketamine can cause moderate to severe psychomotor, cognitive, and residual effects on driving skills. The expert panel stated that the use of ketamine therefore was not compatible with safe driving. As to tolerance, high tolerance was described after long-term exposure.

G. Antihistamines and Antidepressants

We did not find any studies that complied with our inclusion criteria, but some recent review articles have dealt with this topic [10,74,100,106,107].

CONCLUSIONS

Benzodiazepines and Related Drugs

The evidence from the experimental studies reviewed, as well as other reviews and meta-analyses, indicate that all benzodiazepines studied have impairing effects that are dose-related. Tolerance to these effects has only to a limited extent been studied in the experimental reports reviewed. Moderate but incomplete tolerance was suggested in a meta-analysis. Synergistic interaction with alcohol was shown in some studies, in accordance with several review articles.

Cannabis

The reviewed studies revealed that cannabis can cause dose-dependent impairment of driving skills in both experienced and inexperienced users. Tolerance may develop to many of the effects of cannabis. Additive effects of THC and alcohol have been reported, while other studies found that the combination did not produce such effects.

Opioids

The studies showed that opioids can have some impairing effects on cognitive and psychomotor performance, but the effects seem moderate with no clear dose relation. Tolerance to these effects can develop in chronic opioid users. Synergistic effects between opioids and alcohol has not been shown.

Stimulants

In experimental studies where doses up to 40 mg of amphetamine were administered, both improvement and impairment on performance have been observed, as well as no effects. However, there are indications that higher doses may impair driving-related skills. Tolerance has been reported for amphetamines and MDMA. The effects of combining amphetamines and alcohol in experimental studies are variable.

GHB

Experimental studies have reported dose-dependent cognitive and psychomotor impairment after use of GHB.

Ketamine

Experimental studies reported cognitive and psychomotor impairment after use of ketamine, and dose-dependent impairment was described.

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