JOURNAL OF FORENSIC SCIENCES

J Forensic Sci, March 2012, Vol. 57, No. 2
doi: 10.1111/j.1556-4029.2012.02055.x
Available online at: onlinelibrary.wiley.com

PAPER

TOXICOLOGY

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Driving Under the Influence of Amphetamine-Like Drugs

ABSTRACT: Scientific opinions differ whether the use of stimulants causes deterioration in driving skills. In 1857 of 8709 cases of driving under the influence of drugs, amphetamine-like drugs (amphetamine, methamphetamine, and methylendioxyamphetamine) were present either alone or together with other licit or illicit drugs. In 338 cases, amphetamines were the only psychoactive substance group in plasma at mean, median, and highest concentrations of 0.18, 0.12, and 1.05 mg/L, respectively. A widespread opinion is that after the consumption of amphetamines, centrally stimulating effects with corresponding consequences on safe driving are expected. In contrast, many cases were observed that rather suggested an influence of centrally sedating substances when considering the psycho-physical conditions. Relations between concentration and effect could not be established. The apparent sedation is probably the consequence of sleep deprivation during an amphetamine binge and the after-effects of the drug.

KEYWORDS: forensic science, amphetamines, ecstasy, driving under the influence of drugs, gas chromatography–mass spectrometry, driving ability, exhaustion

Amphetamines are central stimulants and belong to a group of drugs that include prescription medicines and illegally produced amphetamines and methamphetamine (1). Ecstasy is a term for a range of drugs that are similar in structure to 3,4-methylenedioxymethamphetamine (MDMA) or 3,4-methylenedioxyethylamphetamine (MDEA) and cause both stimulating amphetamine effects and hallucinogenic effects. Additionally, there are many further so-called amphetamine-type designer drugs that are widely abused by young people (2,3). Amphetamines suppress feelings like tiredness and hunger, and increase mental alertness and physical energy. In addition, they stimulate mood and increase self-confidence. The therapeutic applications of amphetamines include the treatment for narcolepsy, obesity, and hyperactive behavior in children. However, it is well known that amphetamines are used by truckers and students to stay awake over long periods. MDMA and its analogs act as both stimulants (''dance pills'') and entactogens (emotional disinhibition and increased social communication abilities). It was considered that the effects of amphetamines/ecstasy are influenced by a range of factors and therefore can be different for each person. Things to consider include the quality and dose (there is no quality control on illegally manufactured drugs so manufacturers may substitute a wide range of substances) and especially the consumer's psychological and physical attributes. A widespread opinion is that after the consumption of amphetamines, centrally stimulating effects with corresponding consequences regarding safe driving are to be expected. It is also known that the so-called come down effects (e.g., exhaustion, mood swings, and depression) after using amphetamines may also impair a person's driving ability. Iten (4) specified the typical effects of amphetamine analogs which could have an influence on driving behavior with subdivisions of three main categories (Table 1). Some of the desired acute effects after amphetamine abuse cannot directly be associated with impaired driving behavior, and a few effects can actually be classified as positive. Summarized from different sources (4–10) as a general guide, some of the effects of amphetamines that can affect a person's driving ability include the following:

1. attention difficulties and a tendency to fidget;
2. feeling disorientated;
3. lack of coordination;
4. impaired ability to react appropriately and to safely control a vehicle;
5. aggressive and dangerous driving and an increased chance of taking unnecessary risks;
6. over-confidence in driving skills, not necessarily supported by an actual improvement in driving ability;
7. drowsiness as the amphetamine's effects wear off and the driver risks falling asleep (rebound fatigue).

Recently, Raes et al. (8) summarized some studies concerning amphetamines and driving. According to Silber et al. (11) during tests in a driving simulator, the intake of dexamphetamine (0.42 mg/kg) caused a decrease in the overall simulated driving performance during daytime by inducing problems such as incorrect signaling, failing to stop at a red traffic light, and slow reaction times. However, it should be kept in mind that the three errors in driving that were identified were the only three of over 30 measures of driving that were affected and were probably not significant. Brookhuis et al. (12) conducted driving simulator tests in a group of young people who had indicated that they regularly used MDMA. They were tested shortly after the use of MDMA, before going to a party, and then again while sober on a control night at a comparable time. Under the influence of MDMA, subjects drove faster, but only in built-up areas with a speed limit of 50 km/h. Speed variance increased as well, both in the city and on the

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Received 19 Mar. 2010; and in revised form 7 Oct. 2010; accepted 25 Nov. 2010.

TABLE 1—*Amphetamine effects according to Iten (4).*

	Impairment of driving ability
Desired acute effects	
Enhanced physical performance (alertness, stimulation, motivation)	No
Good emotions (difficult to specify)	No
Enhanced ability to communicate	No
Enhanced perception	No
Expanded consciousness	No/Yes
Internal calm, relaxation	No/Yes
Enhanced feeling of self-worth	Yes/No
Euphoria	Yes/No
Altered percipiences (esp. ecstasy)	Yes
Alienation of reality	Yes
Disinhibition	Yes
Increased readiness to assume risk	Yes
Undesired acute effects	
Perspiration, dry mouth	No
Enhancement of blood pressure, heart rate, body temperature	No/Yes
Mydriasis	Yes/No
Nausea, vomiting	Yes
Headache	Yes
Muscle cramps (esp. maxillary cramps)	Yes
Agitation, anxiety	Yes
Disturbances of concentration and alertness	Yes
Confusion	Yes
Psychoses	Yes
Undesired after-effects	
Fatigue	Yes
Exhaustion	Yes
Physical collapse	Yes
Loss of motivation, failing of impulsion, weakness	Yes
Loss of attention	Yes
Lack of concentration	Yes
Depressive mood	Yes

motorway. Lateral control and gap acceptance behavior were not affected. Crashes occurred during two of the 20 control rides and four times while under the influence of MDMA—a 100%—increase. In Norway, Gustavsen et al. (13) studied the concentration–effect relationship between blood amphetamine concentrations and impairment in selected cases, with amphetamine or methamphetamine as the only drug present in blood samples from impaired drivers. According to the police physician, 27% were judged as "not impaired," while 73% were judged as "impaired." A positive relationship was found between blood amphetamine concentration and impairment, but it reached a ceiling at concentrations of 0.27–0.53 mg/L. It has to be taken into consideration that suspected drivers in this study were mostly apprehended as a result of conspicuous driving or involvement in traffic accidents, indicating poor driving performance. This resulted in a high percentage of the drivers being judged impaired compared to experimental studies. In a Canadian study, it was demonstrated that driving under the influence of amphetamines is associated with an increased accident risk of 12.8 (odds ratio [OR]; 95% CI, 3.0–54.0) (14). In a responsibility analysis by Drummer et al. (15), the risks associated solely with amphetamines were not calculated; instead, a group of substances acting as stimulants, namely amphetamine, methamphetamine, MDMA, ephedrine, pseudoephedrine, phentermine, and cocaine, were examined. There was no significant association between stimulant use and crash responsibility. However, when truckers were considered as a discrete driver type, the OR increased to 8.8 and was of borderline statistical significance (95% CI, 1.0–77.8). In a comprehensive study, Lamers et al. (16) showed that MDMA improved psychomotor performance, such as movement speed and tracking performance in a single task, as well as with divided attention. However, MDMA impaired the ability to predict object movement under divided attention, which indicated impairment of particular performance skills relevant to driving. In a further study, MDMA use appeared to have improved certain aspects of the driving tasks under consideration, such as road-tracking performance, but reduced performance in other aspects, such as accuracy of speed adaptation during car-following performance (17). Nocturnal doses of MDMA produced impairments of tracking performance and divided attention throughout the night that were additive to performance impairment produced by sleep loss (18). Furthermore, stimulants like MDMA moderated the impairing effects of a low dose of alcohol on road-tracking performance but could not overcome alcohol-induced impairment on other aspects of driving behavior (19). It was demonstrated that the central nervous system stimulant effects of MDMA were never sufficient to overcome alcohol-induced impairment of impulse-control or risk-tasking behavior (20).

In our routine laboratory, accredited according to ISO EN 17025 for forensic purposes, we analyze plasma samples for the presence of various amphetamines in cases of driving under the influence of drugs (DUID), using a validated gas chromatographic–mass spectrometric (GC–MS) procedure. Analytical results were retrospectively compared with further information from police observation reports and medical examinations.

Materials and Methods

Chemicals

All drug standards and deuterated internal standards were purchased from Promochem (Wesel, Germany). *N*-methyl-(*N*,*N*-bistrifluoroacetamide) (MBTFA) was purchased from Macherey–Nagel (Dueren, Germany), and all other chemicals were from Merck (Darmstadt, Germany).

Sample Preparation

After the addition of 100 μL of the deuterated internal standard mixture (200 ng/mL of amphetamine-d_5, methamphetamine-d_{11}, methylenedioxyamphetamine-d_5, methylendioxymethamphetamine-d_5, and methylenedioxyethylamphetamine-d_5 in methanol), 30 μL of 2 M sodium hydroxide solution was added to 200 μL of plasma, and the mixture was extracted with 500 μL of *n*-hexane. Subsequently, 160 μL of the organic layer was transferred into a 2-mL vial. After the addition of 40 μL of MBTFA and trifluoroacetylation at 70°C for 20 min, the solution was analyzed by GC–MS in the selected ion monitoring mode.

GC–MS Analysis—An Agilent 5890 Series II Plus GC (Waldbronn, Germany) coupled to a 5972 mass selective detector was used for analysis. Data acquisition and data analysis were performed on the Chemstation software (Agilent). A fused-silica capillary column HP-5MS (30 m × 0.25 mm, 0.25 μm film thickness) (Agilent) was used with a flow rate of 1 mL helium/min after splitless injection at an injector temperature of 280°C. The temperature started at 80°C, held for 1 min, increased by 10°C/min up to 280°C, and then was held for 2 min. The ions monitored were 91, 118, and 140 amu for amphetamine; 110, 118, and 154 amu for methamphetamine; 135, 162, and 275 amu for methylenedioxyamphetamine; 110, 135, and 154 amu for MDMA; and 140, 168, and 303 amu for MDEA. The procedure was fully validated according to the guidelines for forensic purposes (21,22) and revealed limits

TABLE 2—*Co-consumption in all DUID cases positive for amphetamine-like drugs (*n = *1857).*

Cannabinoids (%)	Cocaine (%)	Opiates (%)	Benzodiazepines (%)	Methadone (%)	Other drugs (%)
59.7	8.2	1.5	2.8	1.1	2.2

of detection for amphetamine-like substances between 0.003 and 0.006 mg/L and limits of quantification between 0.010 and 0.017 mg/L, respectively.

Samples

Blood samples were taken from apprehended drivers suspected of DUID using a 10-mL Vacutainer tube containing 25 mg sodium fluoride and 20 mg potassium oxalate. Sampling was performed in a time frame of 15–137 min after driving a motor vehicle. Normally the blood sample is stored at *c.* 4°C until arrival in our laboratory within 1–3 days (via courier). In our laboratory, the samples are immediately centrifuged and the plasma is stored at −20°C until further analysis.

Statistics

Data analyses were performed by the use of SPSS version 12.0.1 (SPSS Inc., Chicago, IL). The mean, median, and concentration ranges were used as descriptive statistics. Potential differences were examined by the use of the Student's *t*-test, chi-squared test, and Mann–Whitney *U*-test for nonparametric continuous variables.

Results

Amphetamine-type drugs (amphetamine, methamphetamine, MDMA, or MDEA) were present in 1857 of 8709 cases of DUID (21.1 %), either alone or together with other licit or illicit drugs. In none of the cases, a medical use of amphetamine was claimed by the person concerned.

When considering the co-consumption of other drugs, cannabinoids were found in 59.7% of all cases that were positive for amphetamine-like drugs, followed by cocaine/benzoylecgonine in 8.2% of cases (Table 2). Other drugs played a minor role in the present cohort of amphetamine abusers.

The abusers of amphetamine-type drugs were mainly men (92.8%) and tended to be younger than the whole DUID cohort (mean 26.3 vs. 28.4 years in all cases of DUID).

In 338 cases, amphetamines were the only psychoactive substances in the plasma at mean, median, and highest concentrations of 0.181, 0.12, and 1.05 mg/L, respectively (Table 3). The second prominent amphetamine-like drug in the present cohort was MDMA (75 cases without further drugs), followed by MDEA ($n = 12$), whereas methamphetamine-positive cases ($n = 5$) were rare.

In the group who were positive for only amphetamine-type drugs, all cases (with a blood alcohol concentration < 0.3 mg/kg) were summarized, and the concentrations of MDMA, MDEA, and methamphetamine were 1:1 normalized on a molecular basis to the concentration of amphetamine. Furthermore, several diagnoses of a police observation report as well as of a medical examination on the occasion of blood sampling were summarized to allow for the determination of the disposition of the offenders who were more stimulated or probably more sedated. A differentiation was complicated because in many cases, the impairment symptoms documented in the records were not consistent. Symptoms described were indicative of stimulation simultaneously to symptoms for sedating effects. The medical examinations were consistently carried out after police examinations with a time difference between 30 and 125 min. The results are demonstrated in Table 4 and showed no clear concentration–effect relationship. Additionally, there was no correlation between medical and police examinations.

TABLE 3—*DUID cases with amphetamine-like drugs as the only psychoactive substance in plasma.*

Substance	*n*	Median (mg/L)	Mean (mg/L)	Range (mg/L)
Amphetamine	338	0.12	0.181	0.004–1.049
Methamphetamine	5	0.056	0.058	0.015–0.146
MDEA	12	0.13	0.118	0.032–0.42
MDMA	75	0.189	0.223	0.011–1.1

Discussion

In the present study, drugs from the amphetamine group were detected in 1857 of 8709 cases of DUID (21.1%) either alone or together with other licit or illicit drugs. It has to be taken into account that a cohort of drivers was investigated, who were DUID suspects. In general, looking at a group of drivers suspected of DUID, a higher prevalence of licit and illicit drugs can be found compared to roadside surveys. Detection of this group depends on the perception of the police officers, and additionally, there are remarkable differences between countries, probably because of different national road traffic acts and levels of attention to the problem. The prevalence of in the present study is higher than in most other reports, with a rate between 0 and 7% (15,23–38), but in Australia (39), Belgium (40), the Netherlands (41), Norway (42), and Germany (43,44), a similar prevalence was found of amphetamine abuse between 19.7 and 29.3%. In Sweden (45) and also in a study from Belgium (46), the prevalence was actually reported with 59.0 and 54.2%, respectively. It has to be taken into consideration that a positive preselection was made in all of these studies.

In the present cohort, polydrug abuse is widespread, and therefore, the examination of only amphetamine-typical effects is complicated. As described by Nemecek (47), cannabinoids were the most common drugs found in amphetamine abusers, and this is confirmed in the present study followed by cocaine, a further stimulant. It is a well-known phenomenon that amphetamines are used as so-called uppers, often followed by the consumption of centrally sedating drugs, with cannabinoids favored as so-called downers. Similar findings for amphetamine abusers were reported from the Netherlands (41), and also in Switzerland, more than half of the cases involved consumption of mixtures of drugs (36).

It is of interest that the concentrations of amphetamines measured in the present study were lower compared with those of Scandinavian studies. In a population of 6,613 Swedish DUID amphetamine offenders, Jones and Holmgren (48) reported about high amphetamine concentrations in a positive selection with a mean and median of 0.89 and 0.7 mg/L. An abnormally high concentration of 17 mg/L was found without a fatal outcome. In blood samples from 300 DUID suspects with amphetamines as the only drug present, mean, median, and highest concentrations were measured to be 1.0, 0.9, and 3.0 mg/L, respectively (49). In a further

TABLE 4—*Concentration–effect relationship in amphetamine-positive cases (DUID and others like criminal assaults or thievery with mono-intoxication).*

		Police Observation Report*		Medical Examination*	
Concentration range (mg/L)	*n*	Sedated (%)	Stimulated (%)	Sedated (%)	Stimulated (%)
0.004–0.025	48	10.4	20.8	29.2	25.0
0.0251–0.05	56	3.6	14.3	21.4	16.1
0.0501–0.1	89	2.2	20.2	20.2	18.0
0.101–0.25	141	2.1	10.6	25.5	12.8
0.251–1.049	96	2.1	28.1	33.3	35.4
All	430	3.3	18.1	26.0	20.7

*The assessment was made by the authors based on diagnoses of a police observation report as well as of a medical examination. Criteria for stimulation: abrasive, strangely cheerful, talkative, aggressive, provocative, excited, do not keep distance. Criteria for sedation: calm, dull, lethargic, decelerated, clumsy, somnolent, impassive, sedated.

study from Norway, the highest concentration of total amphetamine and methamphetamine in blood was 3.74 mg/L with a median of 0.52 mg/L (13). In 208 DUID cases in the Netherlands, mean, median, and highest concentrations of amphetamines were found to be 0.32, 0.22, and 2.3 mg/L, respectively (50). As also described by Dresen et al. (51), the combination of an amphetamine-based drug with γ-hydroxy butyric acid might be very popular. In Switzerland (36), in cases of DUID, the mean, median, and highest concentration of amphetamines were markedly lower and determined to be 0.063, 0.054, and 0.183 mg/L, respectively. Recently, in a nationwide study, amphetamine was found in a mean concentration of 0.145 mg/L (n = 170), and the range was 0.01–3.50 mg/L (38). In a Finnish population of 153 DUID cases, the median amphetamine concentration in blood was 0.455 mg/L, and in this study, the range was 0.045–2.75 mg/L (52).

The main ingredient of ecstasy is MDMA, which was found in the present study in a mean, median, and highest concentrations of 0.223, 0.189, and 1.1 mg/L, respectively. This can be compared with 87 DUID suspects from the Netherlands in whom the mean, median, and highest concentration of MDMA were 0.35, 0.28, and 1.5 mg/L. In a further investigation (n = 360), a mean, median, and highest concentrations of MDMA were found to be 0.44, 0.33, and 4.0 mg/L, respectively (50). In a previous small German study, the concentrations of MDMA in serum were considerably lower, with a median of 0.076 mg/L and a range of 0.001–0.514 mg/L (53). A report of DUID suspects in Norway (n = 190) found a median MDMA concentration in blood of 0.155 mg/L (range: 0.019–1.14 mg/L), with or without recreational drugs (54). Jones et al. (55) reported MDMA concentrations in blood of Swedish DUID offenders (n = 493) with a mean, median, and highest concentrations of 0.23, 0.1, and 3.5 mg/L, respectively. This can also be compared with 28 DUID suspects from Switzerland in whom the mean, median, and highest concentration of MDMA were 0.388, 0.218, and 2.48 mg/L (36) and a new nationwide study (n = 223) where the concentrations were measured with 0.279, 0.011, and 260 mg/L, respectively (38). From Belgium, MDMA concentrations in blood of drivers between 0.049 and 1.51 mg/L were reported (56).

Verschraagen et al. (50) compared the concentrations of amphetamine-based drugs from postmortem cases with those in the cases of DUID and found lower concentrations in the latter group. However, a great overlap was observed, and therefore, the authors claimed that concentrations should never be used in isolation to establish the cause of death.

In the present study, cases solely positive for amphetamine-type drugs were selected, and several diagnoses of a police observation report as well as of a medical examination on the occasion of blood sampling were summarized to allow a determination to be made about the disposition of offenders who were more stimulated (typical actual amphetamine effects) or probably more sedated. Unlike other drugs used by amphetamine abusers in the medical examination, more impairment symptoms were documented compared to the police observations. A differentiation was complicated because in many cases, the impairment symptoms documented in the records were not consistent. Symptoms were described which were indicative for stimulation simultaneously to symptoms for sedating effects (Table 4). In the police observation report stimulated suspects dominated, whereas in the medical examination, more sedated and more stimulated drivers were found in similar ranges. There was a time difference between the police and the medical examinations, but in our opinion, this cannot explain the differences in findings because the plasma elimination half-life is comparatively long. The measured plasma concentrations showed no relationship with impairment.

Recently, it was demonstrated by Silber et al. (57) that the reports of police observations and medical examinations or standardized field sobriety tests are not sensitive measures for detecting the presence of amphetamines. But it has to be considered that in this study, the administered amphetamine doses were very low; thus, impairment could not be expected. Toennes et al. (43) also evaluated impairment symptoms documented in the police observation reports and medical investigations during blood sampling in the cases of DUID. Subjects with no drugs in their plasma showed higher scores and frequencies of impairment than observed for subjects positive for amphetamines. A nonsignificant relationship between amphetamine concentration and impairment was described by others, with an unexpected negative correlation (nonsignificant) for MDMA abusers (47,58). The most documented distinctive features were dilated pupils with a slow reaction to light, but symptoms of a severe intoxication were seldom reported (47). The combination of amphetamines with other drugs markedly increased the chance of being classified as impaired (43,47). Also, a recent study of Jones (49) failed to find an association between the results of clinical tests of impairment and amphetamine blood concentration levels in apprehended drivers. Development of tolerance owing to exhaustion and fatigue from lack of sleep during an amphetamine binge was seen to be responsible. Additionally, others analyzed deficiencies in the physical and psychological performance noted by police and/or medical examiners in amphetamine-positive cases of DUID and reported the symptoms of exhaustion (59,60). According to Schnabel et al. (60), especially low amphetamine concentrations in blood were found to be related to such symptoms of exhaustion. In contrast to others in a Norwegian study, 73% of drivers under the influence of amphetamines were judged as impaired and only 27% were judged as not impaired (13). The median blood concentrations did not differ significantly between the impaired and the nonimpaired drivers. There was a positive

relationship between amphetamine concentration and impairment, reaching a ceiling at blood amphetamine concentrations of 0.27–0.53 mg/L. Younger drivers were more often judged to be impaired than older drivers at similar blood concentrations. However, the clinical test for impairment by a police physician was not described in detail. The authors claimed that their results could stem from at least two phenomena occurring simultaneously. Together with a positive relationship between impairment and blood concentrations present at rising drug levels, an opposite relationship was assumed between impairment and an "end-of-binge" fatigue in amphetamine abusers. The exhaustion seen at the end of an amphetamine binge is seen to be comparable with the effects of sedative drugs. Such an end-of-binge phenomenon with "come down" effects could contribute to lower concentration–effect relationships described in the present or in other studies. Furthermore, it has to be taken into consideration that suspected drivers in this study were mostly apprehended as a result of conspicuous driving or involvement in traffic accidents, indicating poor driving performance. This resulted in a high percentage of the drivers being judged impaired compared to experimental studies.

In our opinion, the judgment of the psycho-physical performance is very complicated with amphetamine consumers as well as with consumers of other stimulants. As already shown by Iten's (4) listing (Table 1), the (ab)use of amphetamines or other stimulants can cause positive (stimulating) effects on cognitive and psychomotor functions, especially in fatigued persons. Additionally, especially after the consumption of stimulants, a (temporal limited) compensation of typical effects is often to be observed during an official investigation by police officers or physicians. For laymen, typical symptoms of stimulation are expected and symptoms of sedation are often not attributed to typical drug effects. However, considering Iten's (4) listing and further studies, it is conspicuous that not only desired or undesired acute effects after amphetamine abuse can lead to impaired driving behavior but also, or especially, undesired after-effects have to be considered. In Table 5, various intra-individual drug effects of stimulants are demonstrated in two case reports involving the same person. Recently, also Lemos (61) reported about two very different sets of circumstances with drivers under the influence of methamphetamine (one driver drove at low speed and was found to be cooperative, while the other was speeding and was aggressive and violent). As described by Ellinwood and Nikaido (62) early in 1987, a single small dose of stimulants actually can have an initial arousal and performance-enhancing effect (Fig. 1). Higher plasma drug concentration can result in a hyperarousal state and degenerated performance. Toxic doses of stimulants generate hyperexcitability and probably toxic hallucinatory delirium-type states with overwhelming degradation of performance. Finally, drug withdrawal can produce hypersomnolence and fatigue with a different type of performance impairment.

In forensic cases, it has to be considered that, when stimulating effects decrease, negative sensations like fatigue, anxiety, emptiness, and depression appear, and later on, a hangover is experienced with headache, muscle aches, exhaustion, apathy, sweating, nausea, and further effects. Similar to cocaine, the "come down"

TABLE 5—*Demonstration of different intra-individual effects of stimulants in the same person at two different occasions.*

1. A 27-year-old woman was subjected to a routine police check and showed insecurity when alighting from the vehicle, an unsteady walk, and a dazed or drowsy state of awareness. The physician who took the blood sample (47 min later) described an unsteady walk as well as strongly dilated pupils with a delayed light reaction, a disturbed orientation, and a slowed down behavior pattern. A chemical–toxicological analysis provided the following findings: amphetamine 0.163 mg/L, benzoylecgonine 0.072 mg/L, and THC-COOH 0.019 mg/L.
2. In a second case, the same woman drove to a supermarket by car and committed a theft. According to police, she was loquacious, aggressive, and completely mad, with a volatile way of thinking. The behavior has been completely inappropriate, and there were no other findings. A chemical–toxicological analysis provided the following findings: amphetamine 0.37 mg/L, MDMA 0.564 mg/L; MDA 0.045 mg/L, and THC-COOH 0.388 mg/L (THC not present).

While in the first case, the end-of-binge fatigue has to be considered as a result of a stimulants' consumption probably some time after the last abuse, the stimulating effects dominated in the second incident with aggressiveness and typical loss of inhibition.

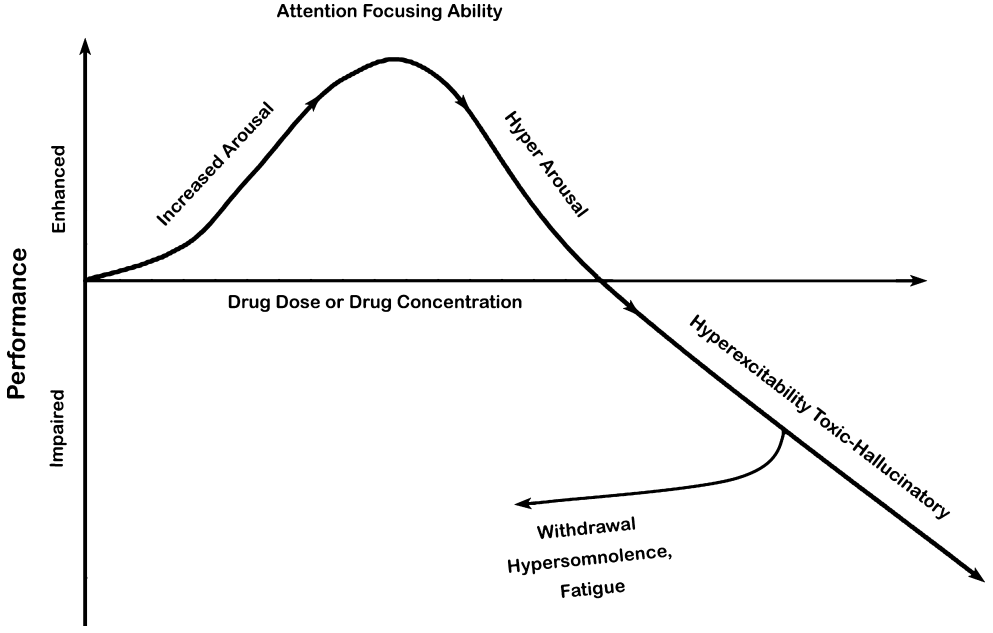

FIG. 1—*Relationship between the drug concentration and the behavioral effects of stimulants: an initial improvement in performance is followed by performance impairment and during drug withdrawal. Modified according to (62).*

effects (exhaustion, difficulty in concentrating, irritability, and depression) after using amphetamines or other stimulants may also impair a person's driving ability. Drivers suffering from drug-induced exhaustion also tend to drive less safely. The apparent sedation is probably a consequence of sleep deprivation during an amphetamine binge and the after-effects of the drug. Besides, exhaustion is not simply to be expected only with low drug concentrations in the blood, but can occur, for example, with high-dose consumption or long-term consumption, with quite relevant and higher substance concentration. Therefore, a concentration–effect relation is not to be expected and makes it nearly impossible to give a scientific definition of clear threshold plasma concentrations for impairment caused by stimulative drugs abused while driving.

References

1. Musshoff F. Illegal or legitimate use? Precursor compounds to amphetamine and methamphetamine Drug Metab Rev 2000;32:15–44.
2. Kraemer T, Maurer HH. Toxicokinetics of amphetamines: metabolism and toxicokinetic data of designer drugs, amphetamine, methamphetamine, and their N-alkyl derivatives. Ther Drug Monit 2002;24:277–89.
3. Staack RF, Maurer HH. Metabolism of designer drugs of abuse. Curr Drug Metab 2005;6:259–74.
4. Iten PX. Designer-Drogen vom Ecstasy-Typ. Wiesbaden, Germany: Abbott, 1998;31–8.
5. Maes V, Charlier C, Grenez O, Verstraete A. Rosita EU research project. Deliverable 1: drugs and medicines that are suspected to have a detrimental effect on road user performance, 1999;5–44, http://www.transport-research.info/Upload/documents/200310/ rositarep.pdf (accessed June 20, 2010).
6. Australian Drug Foundation. Drugs and driving, http://www.drugsdriving.adf.org.au (accessed June 20, 2010).
7. Austrian Road Safety Board. Preventative measures to prevent driving while under the influence of alcohol/drugs. Wien, Austria: Kuratorium für Verkehrssicherheit, 2003.
8. Raes E, van den Neste T, Verstraete A, Lopez D, Hughes B, Griffiths P. Drug use, impaired driving and traffic accidents. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2008.
9. Madea B, Dettmeyer R, with collaboration of Musshoff F. Basiswissen Rechtsmedizin. Heidelberg, Germany: Springer Verlag, 2007.
10. Madea B, Musshoff F, Berghaus G. Verkehrsmedizin. Cologne, Germany: Deutscher Ärzteverlag, 2007.
11. Silber BY, Papafotiou K, Croft RJ, Ogden E, Swann P, Stough C. The effects of dexamphetamine on simulated driving performance. Psychopharmacology (Berl) 2005;179:536–43.
12. Brookhuis KA, de Waard D, Samyn N. Effects of MDMA (ecstasy), and multiple drugs use on (simulated) driving performance and traffic safety. Psychopharmacology (Berl) 2004;173:440–5.
13. Gustavsen I, Mørland J, Bramness JG. Impairment related to blood amphetamine and/or methamphetamine concentrations in suspected drugged drivers. Accid Anal Prev 2006;38:490–5.
14. Dussault C, Brault M, Bouchard J, Lemire AM. The contribution of alcohol and other drugs among fatally injured drivers in Québec: some preliminary results. Proceedings of the 16th International Conference on Alcohol, Drugs, and Traffic Safety; 2002 Aug 4–9; Montreal, Canada: La Societe deI'Assurance Automobile du Quebec, 2002.
15. Drummer OH, Gerostamoulos J, Batziris H, Chu M, Caplehorn J, Robertson MD, et al. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. Accid Anal Prev 2004;36:239–48.
16. Lamers CT, Ramaekers JG, Muntjewerff ND, Sikkema KL, Samyn N, Read NL, et al. Dissociable effects of a single dose of ecstasy (MDMA) on psychomotor skills and attentional performance. J Psychopharmacol 2003;17:379–87.
17. Ramaekers JG, Kuypers KP, Samyn N. Stimulant effects of 3,4-methylenedioxymethamphetamine (MDMA) 75 mg and methylphenidate 20 mg on actual driving during intoxication and withdrawal. Addiction 2006;101:1614–21.
18. Kuypers KP, Wingen M, Samyn N, Limbert N, Ramaekers JG. Acute effects of nocturnal doses of MDMA on measures of impulsivity and psychomotor performance throughout the night. Psychopharmacology (Berl) 2007;192:111–9.
19. Kuypers KP, Samyn N, Ramaekers JG. MDMA and alcohol effects, combined and alone, on objective and subjective measures of actual driving performance and psychomotor function. Psychopharmacology (Berl) 2006;187:467–75.
20. Ramaekers JG, Kuypers KP. Acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on behavioral measures of impulsivity: alone and in combination with alcohol. Neuropsychopharmacology 2006;31:1048–55.
21. Peters FT, Drummer OH, Musshoff F. Validation of new methods. Forensic Sci Int 2007;165:216–24.
22. Society of Toxicological and Forensic Chemistry (GTFCh). Richtlinie der GTFCh zur Qualitätssicherung bei forensisch-toxikologischen Untersuchungen und Anforderungen an die Validierung von Analysenmethoden, http://www. gtfch. org/cms/index.php/guidelines?Itemid=126 (accessed June 20, 2010).
23. Longo MC, Hunter CE, Lokan RJ, White JM, White MA. The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability: part ii: the relationship between drug prevalence and drug concentration, and driver culpability. Accid Anal Prev 2000;32:623–32.
24. Kintz P, Cirimele V, Mairot F, Muhlmann M, Ludes B. Drug tests on 198 drivers involved in an accident. Presse Med 2000;29:1275–8.
25. Mura P, Kintz P, Ludes B, Gaulier JM, Marquet P, Martin-Dupont S, et al. Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subjects: results of a French collaborative study. Forensic Sci Int 2003;133:79–85.
26. Michael WJ, Flegel R, Atkins R, Cangianelli LA, Cooper C, Welsh C, et al. Drug and alcohol use among drivers admitted to a Level-1 trauma center. Accid Anal Prev 2005;37:894–901.
27. Dussault C, Brault M, Bouchard J, Lemire AM. The contribution of alcohol and other drugs among fatally injured drivers in Québec: final results. In: Oliver J, Williams P, Clayton A, editors. Proceedings of the 17th International Conference on Alcohol, Drugs, and Traffic Safety; 2004 Aug 8–13; Glasgow, Scotland. Ann Arbor, MI: The International Council on Alcohol, Drugs and Traffic Safety, 2004.
28. Mura P, Chatelain C, Dumestre V, Gaulier JM, Ghysel MH, Lacroix C, et al. Use of drugs of abuse in less than 30-year-old drivers killed in a road crash in France: a spectacular increase for cannabis, cocaine and amphetamines. Forensic Sci Int 2006;160:168–72.
29. Vignali C, Groppi A, Polettini A, Valli A, Sali A, Cancelli B, Montagna M. Drugs and driving. Toxicological findings in 119 fatally injured drivers. In: Novakova E, Habrdova V, editors. Proceedings of the 39th International Meeting of the International Association of Forensic Toxicologists (TIAFT); 2001 Aug 26–30; Prague, Czech Republic: Faculty of Medicine Charles University, 2001;368–73.
30. Soderstrom CA, Ballesteros MF, Dischinger PC, Kerns TJ, Flint RD, Smith GS. Alcohol/drug abuse, driving convictions, and risk-taking dispositions among trauma center patients. Accid Anal Prev 2001;33:771–82.
31. del Rio CM, Gomez J, Sancho M, Alvarez FJ. Alcohol, illicit drugs and medicinal drugs in fatally injured drivers in Spain between 1991 and 2000. Forensic Sci Int 2002;127:63–70.
32. Holmgren P, Holmgren A, Ahlner J. Alcohol and drugs in drivers fatally injured in traffic accidents in Sweden during the years 2000–2002. Forensic Sci Int 2005;151:11–7.
33. Assum T, Mathijssen MPM, Houwing S. The prevalence of drug driving and relative risk estimations. A study conducted in the Netherlands, Norway and United Kingdom; immortal deliverable D-R4.2. Vienna, Austria: Austrian Road Safety Board, 2005.
34. Logan BK, Schwilke EW. Changing patterns of alcohol and drug use in fatally injured drivers in Washington State 1992–2002. In: Oliver J, Williams P, Clayton A, editors. Proceedings of the 17th International Conference on Alcohol, Drugs, and Traffic Safety; 2004 Aug 8–13; Glasgow, Scotland. Ann Arbor, MI: The International Council on Alcohol, Drugs and Traffic Safety, 2004.
35. Logan BK. Adverse effects of stimulants and cannabis on driving. 17th Triennial Meeting of the International Association of Forensic Sciences (IAFS); 2005 Aug 21–26; Hong Kong. Hong Kong: IAFS, 2005.
36. Augsburger M, Donze N, Menetrey A, Brossard C, Sporkert F, Giroud C, et al. Concentration of drugs in blood of suspected impaired drivers. Forensic Sci Int 2005;153:11–5.
37. Gjerde H, Normann PT, Pettersen BS, Assum T, Aldrin M, Johansen U, et al. Prevalence of alcohol and drugs among Norwegian motor vehicle drivers: a roadside survey. Accid Anal Prev 2008;40:1765–72.
38. Senna MC, Augsburger M, Aebi B, Briellmann TA, Donzé N, Dubugnon JL, et al. First nationwide study on driving under the influence of drugs in Switzerland. Forensic Sci Int 2010;198:11–6.

39. Kotsos A, Gerostamoulos J, Boorman M, Drummer OH. Prevalence of drugs in Victorian impaired drivers. Proceedings of the 41st Meeting of the International Association of Forensic Toxicologists (TIAFT); 2003 Nov 16–20; Melbourne, Australia. Melbourne, Australia: TIAFT, 2003.
40. Raes E, Verstraete AG. Usefulness of roadside urine drug screening in drivers suspected of driving under the influence of drugs (DUID). J Anal Toxicol 2005;29:632–6.
41. Smink BE, Ruiter B, Lusthof KJ, Zweipfenning PG. Driving under the influence of alcohol and/or drugs in the Netherlands 1995–1998 in view of the German and Belgian legislation. Forensic Sci Int 2001;120:195–203.
42. Christophersen AS. The occurence of drugged driving in Norway—existing problems and solutions. Blutalkohol 2000;37:20–7.
43. Toennes SW, Kauert GF, Steinmeyer S, Moeller MR. Driving under the influence of drugs—evaluation of analytical data of drugs in oral fluid, serum and urine, and correlation with impairment symptoms. Forensic Sci Int 2005;152:149–55.
44. Wollersen H, Müller C, Musshoff F, Madea B. Drogen- und Arzneimittelbeeinflussung von Verkehrsteilnehmern. Blutalkohol 2008; 45:89–102.
45. Jones AW. Driving under the influence of drugs in Sweden with zero concentration limits in blood for controlled substances. Traffic Inj Prev 2005;6:317–22.
46. Maes V, Samyn N, Willekens M, De Boeck G, Verstraete A. 'Stupefiants et conduite automobile – les actions realisees en Belgique.' Ann Toxicol Analyt 2003;15:128–37.
47. Nemecek D. Amphetamin- und Amphetaminderivat-Konsum und Teilnahme am Straßenverkehr. Gibt es eine Beziehung zwischen Wirkung und Wirkstoffkonzentration im Blut? [Thesis]. Düsseldorf (Germany): Heinrich-Heine University, 2008.
48. Jones AW, Holmgren A. Abnormally high concentrations of amphetamine in blood of impaired drivers. J Forensic Sci 2005;50:1215–20.
49. Jones AW. Age- and gender-related differences in blood amphetamine concentrations in apprehended drivers: lack of association with clinical evidence of impairment. Addiction 2007;102:1085–91.
50. Verschraagen M, Maes A, Ruiter B, Bosman IJ, Smink BE, Lusthof KJ. Post-mortem cases involving amphetamine-based drugs in The Netherlands. Comparison with driving under the influence cases. Forensic Sci Int 2007;170:163–70.
51. Dresen S, Kempf J, Weinmann W. Prevalence of gamma-hydroxybutyrate (GHB) in serum samples of amphetamine, metamphetamine and ecstasy impaired drivers. Forensic Sci Int 2007;173:112–6.
52. Engblom C, Gunnar T, Rantanen A, Lillsunde P. Driving under the influence of drugs—amphetamine concentrations in oral fluid and whole blood samples. J Anal Toxicol 2007;31:276–80.
53. Moeller MR, Hartung M. Ecstasy and related substances—serum levels in impaired drivers. J Anal Toxicol 1997;21:591–6.
54. Hausken AM, Skurtveit S, Christophersen AS. Characteristics of drivers testing positive for heroin or ecstasy in Norway. Traffic Inj Prev 2004;5:107–11.
55. Jones AW, Holmgren A, Kugelberg FC. Driving under the influence of central stimulant amines: age and gender differences in concentrations of amphetamine, methamphetamine, and ecstasy in blood. J Stud Alcohol Drugs 2008;69:202–8.
56. Samyn N, Viaene B, Laeremans G, De Boeck G, Maes V. First experience with the enforcement of the new per se DUID legislation in Belgium. In: Rasanen I, editor. Proceedings of the 38th Meeting of the International Association of Forensic Toxicologists (TIAFT); 2000 Aug 13–17; Helsinki, Finland. Helsinki, Finland: TIAFT, 2000;106–16.
57. Silber BY, Papafotiou K, Croft RJ, Stough CK. An evaluation of the sensitivity of the standardised field sobriety tests to detect the presence of amphetamine. Psychopharmacology (Berl) 2005;182:153–9.
58. Daldrup T. Neue Erkenntnisse zur Beurteilung der Blutbefunde. Blutalkohol 2008;45:S2–10.
59. Musshoff F, Wollersen H, Madea B. Über die Beeinträchtigung der Fahrsicherheit nach Konsum von Amphetaminen. In: Mattern R, editor. Kongressbericht der Deutschen Gesellschaft für Verkehrsmedizin e.V., Berichte der Bundesanstalt für straßenwesen, mensch und sicherheit, Heft M 195, Wirtschaftsverlag NW, Bremerhaven, 2008;157–60.
60. Schnabel A, Niess C, Kauert G. Die Erschöpfungsreaktion nach Amphetaminkonsum und ihre Auswirkungen auf die Fahrtüchtigkeit. Rechtsmed 2000;10:86–9.
61. Lemos NP. Methamphetamine and driving. Sci Justice 2009;49:247–9.
62. Ellinwood EH, Nikaido AM. Stimulant induced impairment: a perspective across dose and duration of use. Alco Drugs Driving 1987;3: 19–24.

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