Methamphetamine — Effects on Human Performance and Behavior

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ABSTRACT: Methamphetamine is a popular recreational drug that has also had some historical use as a therapeutic agent. Its effect profile is complex, with stimulant, alerting effects during acute low-dose administration, progressively more disorienting effects on cognition, reasoning, and psychomotor ability with increased dosing and duration of use, and a depressant-like profile during withdrawal, often compounded by delusions and psychotic episodes, especially after high-dose or chronic use. This manuscript reviews the synthetic, structural, and analytical chemistry of the drug; the pharmacology of its central and peripheral effects; its pharmacokinetics following various routes of administration and dosage regimens; and its pharmacodynamics in both acute and chronic administration and therapeutic and recreational doses, noting in particular its effects on judgment, decision making, risk-taking, cognition and psychomotor performance, and violence. Finally, the review considers the issue of how these various effects can impact driving ability and can contribute to impairment. From the material reviewed it is concluded that the use of methamphetamine in anything other than low-dose, therapeutic administration with medical oversight raises the likelihood of some impairment of performance in complex psychomotor tasks such as driving.

KEY WORDS: Driving, forensic toxicology, human performance, impairment, methamphetamine.

INTRODUCTION

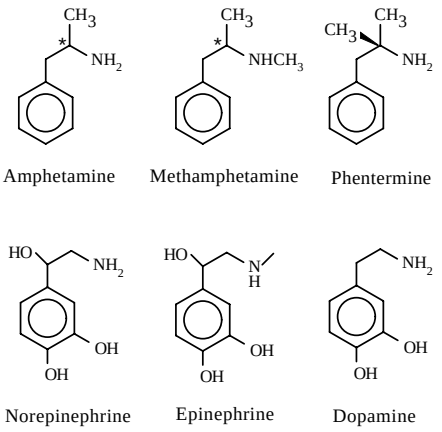
Methamphetamine is a central nervous system stimulant with some legitimate therapeutic uses, but it has a tremendous potential for abuse. It has a history as a periodically popular drug of abuse, which at the time of writing is undergoing a resurgence in popularity [6,15]. It is truly a mind-altering drug, and as such, its use by drivers constitutes a real public safety and traffic safety concern. This review attempts to summarize the chemistry, pharmacology, pharmacokinetics, pharmacodynamics, and toxicology of the drug, and its specific effects on human performance and behavior. The review is designed to be a summary and synopsis of major forensic issues arising from use of this drug, and the reader is strongly encouraged to seek out the primary literature cited for the detail necessarily omitted in any review.

I. CHEMISTRY

A. Nomenclature

Methamphetamine ($C_{10}H_{15}N$) (**Structure 1**), is the common name for *N*,α-dimethylphenethylamine, also referred to as desoxyephedrine, methylamphetamine, phenylisopropylmethylamine, and a variety of other similar systematic names. Methamphetamine is an amphetamine derivative and belongs to the class of amphetamines. The drug was first synthesized in Japan in 1919 by Ogata [84], patented in 1920, and later licensed to Burroughs Wellcome, who marketed it as the anorectic Methedrine®.

The technical nomenclature for methamphetamine is discussed below, but there are a variety of popular terms including meth, crystal meth, crystal, ice, speed, whiz, and crank. No term is specific for particular grade or chemical product, although these terms are generally reserved for illicit preparations, as opposed to diverted pharmaceuticals. Frequently, drugs sold as methamphetamine may in fact contain no methamphetamine at all, and are actually substitutes such as caffeine, ephedrine, pseudoephedrine, or even cocaine, depending on local drug availability.



Structure 1. Structures of the synthetic sympathomimetics amphetamine, methamphetamine, and phentermine, together with those of the neurotransmitters whose release they are believed to promote. (* indicates asymmetric carbon atoms on amphetamine and methamphetamine.)

B. Chemical Properties

As discussed below, methamphetamine exists in two isomeric forms, dextro (*d*-), and levo (*l*-), and these may appear as prefixes to any of the terms discussed above to denote the particular isomer. The free base (pKa 9.9) has a molecular weight of 149.24 a.m.u., and is a liquid at room temperature, so is invariably supplied and used as the hydrochloride salt ($C_{10}H_{16}ClN$, 185.74 a.m.u.), which has a melting point of 170–175 ºC. Of note is the fact that this salt, unlike the hydrochloride salt of cocaine, volatilizes without pyrolysis at 300–305 ºC, a temperature readily achieved in a butane lighter flame, meaning that it can be smoked in the salt form without the tedious conversion to the base required in order to smoke cocaine.

C. Stereochemistry

The configuration at the chiral center dictates the CNS activity of the product, with *d*-amphetamine (sometimes denoted as S-(+)-amphetamine) having the greatest CNS stimulant effects, 3-4 times that of the *l*-isomer [41]. The terms *d*- and *l*- refer to the dextrorotatory or levorotatory properties with respect to plane-polarized light. Pure *d*-methamphetamine has an [α]D25 of +14 to +20º [73]. Determination of the enantiomeric ratio is helpful in determining whether the drug may have originated from licit sources (*l*-desoxyephedrine is sold over the counter in the U.S. as the nasal decongestant, Vicks® Inhaler), or illicit or diverted sources. *d*-Methamphetamine is a legal schedule II [1] prescription drug (Desoxyn®) [88] and the predominant form in many current syntheses (discussed below), while the racemic mixture arises from certain specific illicit syntheses.

D. Synthesis

Prior to 1980, the popular methamphetamine synthesis was from phenyl-2-propanone (P2P, phenylacetone) by reductive amination with methylamine over an aluminum amalgam catalyst. At that time, P2P was available through commercial sources with no restrictions, but had significant neurotoxicity, making the labs dangerous to both investigators and the "meth cooks" that operated them. The product of the reaction was a racemic mixture of *d*- and *l*-methamphetamine. Controls placed on P2P in the early 1980s imposed the need for additional steps to synthesize this precursor, and other syntheses involving more readily obtainable starting materials became popular. Two are briefly described here.

The first is a reduction of *l*-ephedrine or *d*-pseudoephedrine over red phosphorus with hydroiodic acid. The enantiospecific product with either precursor is *d*-methamphetamine, with yields of 54–82%. The red phosphorus is obtained from matchbook striker plates or road flares, and although the sale of hydroiodic acid is now restricted, it can be synthesized with little difficulty from iodine.

The second method also results in an enantiospecific product, *d*-methamphetamine, and involves the reduction of the same *l*-ephedrine or *d*-pseudoephedrine precursors using either sodium or lithium metal in condensed liquid ammonia. The lithium can be obtained from lithium batteries, sodium from electrolytic reduction of molten sodium hydroxide, and liquid ammonia from agricultural or specialty gas suppliers. The substitution of phenylpropanolamine as the precursor in either synthesis yields amphetamine.

Obviously, fire and health risks from these reagents are significant to investigators, firefighters, and others finding the remains of a laboratory by accident. These latter two syntheses are suitable for small-scale production. Recipes and directions for obtaining precursors are available on the Internet and have contributed to the growing popularity of the drug.

E. Analysis

Methamphetamine is a prototypical basic drug (pKa 9.9), and is readily extracted from biological material into organic solvents at alkaline pH. It is readily soluble in chloroform, *N*-butyl chloride, ethyl acetate, and diethyl ether, and is extracted in most common protocols designed to isolate alkaloidal and basic drugs. It also readily back-extracts into acid, and back into organic solvents without significant loss. Because of its volatility, however, it can be lost during a dry-down or evaporation step if that is part of the procedure. This loss can be avoided by the addition of a small amount of hydrochloric acid during the evaporation step, or the addition of a less volatile "keeper" solvent such as dimethylformamide (DMF).

Methamphetamine is readily analyzed by gas chromatography (GC), and this is the most popular method in use today for analysis of methamphetamine in biological material. Its poor UV absorption properties make it an unsuitable candidate for high performance liquid chromatography (HPLC) with ultraviolet (UV) detection, and it has no native fluorescence, and no significant oxidative electrochemical properties at low voltages.

When analyzed without derivatization, as is commonly done in GC drug screening, methamphetamine is readily eluted from most stationary phases at low temperatures (~50 ºC) due to its low molecular weight, but its basicity results in peak-tailing on some phases. Because of its early elution time, care should be taken in underivatized

GC analysis where the detector is initially turned off to allow elution of the solvent front because the drug may elute before the detector turns on. Standards for this drug and its major metabolite, amphetamine, should be run frequently, especially following column maintenance or changes in GC conditions. Its low molecular weight, the low intensity of its mass fragments in electron impact mode, and the structural similarity of many endogenous and exogenous compounds mean that the mass spectrum of methamphetamine is not as highly characteristic as many others. For example, phentermine (Structure 1), a structural isomer of methamphetamine, has a very similar mass spectrum. Care should therefore be taken when performing analysis of methamphetamine to check both the retention time of this drug and its analogs, and to carefully review the mass spectra for consistency.

There is evidence that at very high concentrations, ephedrine or pseudoephedrine may be converted to methamphetamine in the GC injection port [10,48]. A procedure involving periodate pretreatment has been described which eliminates this interference [31]. Other researchers have reported that methamphetamine can be demethylated to amphetamine during this periodate treatment, and recommend the use of pH 6.2 to avoid this [85]. The Substance Abuse and Mental Health Services Administration (SAMHSA, formerly the National Institute on Drug Abuse, NIDA) also requires that in regulated urine drug testing, at least 0.200 mg/L of amphetamine be present before a methamphetamine result can be reported [78]. In a non-regulated setting, where this criterion is not typically applied, but where ephedrine is shown to be present in great excess of methamphetamine, there should be a careful review of the procedure and data.

The issue of lack of specificity of the methamphetamine mass spectrum can be resolved by derivatization [106]. Many methods have been published for the analysis of methamphetamine and related compounds [2,26,40,47, 71]; the reader is encouraged to review these further.

II. PHARMACOLOGY

The pharmacology of the amphetamines is complex, and involves both central and peripheral actions. The summary presented here is necessarily brief, and a review of the pharmacology of neurohumoral transmission in a comprehensive pharmacology textbook is encouraged.

Methamphetamine is a sympathomimetic drug, meaning that it mimics endogenous transmitters in the sympathetic nervous system by interaction with their receptors. The prototypical sympathetic neurotransmitters are the catecholamines, norepinephrine, dopamine, and epinephrine, and the structural similarity of methamphetamine is clear (Structure 1). Specifically, methamphetamine interacts with presynaptic receptors by competitive antagonism, and has minimal, if any, effect as an agonist at postsynaptic receptors.

A. CNS Effects

The amphetamines' potent central nervous system (CNS) stimulating effects appear to result by promoting the release of biogenic amines from their stores in the nerve terminals, and there is some association between specific aspects of the amphetamine experience, and neurophysiological structure and chemistry [29,41].

Enhanced release of norepinephrine from central noradrenergic neurons appears to be responsible for the alerting and anorectic effects of the amphetamines, and, together with dopamine release from dopaminergic nerve terminals, for the locomotor stimulating effects. The stereotyped repetitive behavior characterized by higher doses of amphetamines is also a feature of dopamine release, particularly in the neostriatum. At yet higher doses, dopamine release in the mesolimbic system and enhanced release of 5-hydroxytryptamine (5-HT, serotonin) in tryptaminergic neurons may be responsible for both disturbances of perception and frank psychotic behavior [29].

High-dose methamphetamine administration leads to decreases in brain levels of the neurotransmitters dopamine and serotonin (5-HT), and a reduction in the activity of the enzymes responsible for their synthesis (tyrosine dehydroxylase and tryptophan hydroxylase, respectively).

Both acute and chronic administration of methamphetamine in an in vitro system caused a decrease in the rate of dopamine and 5-HT uptake into the striatum as soon as 30 minutes after exposure to the drug [36,60]. The effect was reversible and persisted less than 24 h, and could not be extinguished by washing the drug out of the synaptosomes. The transporter activity returned to normal after 24 h, but declined again after eight days, suggesting a second distinct effect, that of neurotoxicity and associated terminal degeneration. There is evidence that other transporter systems such as norepinephrine are also affected, but by a different mechanism, since washing residual methamphetamine out of the cell preparations did eliminate the effect [44].

Tolerance to the CNS effects of amphetamines is pronounced, and in therapeutic use, a course beyond six weeks is not recommended. Gygi et al. [42] demonstrated that methamphetamine concentrations in the brains of rats receiving a long-term methamphetamine pretreatment were decreased compared to non-exposed animals when exposed to a subsequent high-dose methamphetamine challenge. In the same animals, the plasma concentrations

in the exposed animals were higher than in the non-exposed animals following the same challenge. This suggests that tolerance is not principally due to enhanced metabolism or increased renal clearance of methamphetamine, but rather to changes in the structures responsible for uptake. Using a rat model, other workers [93] have also shown that methamphetamine's effects are not reliably predicted from serum concentrations. In the first hour following intravenous administration, brain concentrations are eight times higher than in the serum. An examination of methamphetamine distribution in the brains of decedents from methamphetamine-related deaths has shown little difference in distribution between dopamine rich and dopamine poor areas [57].

Segal and Kuczenski [97] have reported a dopamine/behavioral response to low-dose amphetamine and methamphetamine challenges in animals withdrawn from escalating dose-binge treatment. They suggest that these effects may be linked to the induction of stimulant psychosis in sensitized animals, and by extension in high-dose amphetamine abusers. Other researchers [110] have more recently reported that sensitization to flashbacks can become induced in chronic users, lowering the threshold for reoccurrence of psychotic episodes. Flashbacks are then triggered by stressors including social interaction, conflict, fear of imprisonment, discipline, family pressure, and somatic discomfort. Those experiencing flashbacks reported frightening auditory and visual hallucinations including dead bodies, ghosts, delusions of being attacked, and being followed or pursued.

B. Peripheral Effects

Peripheral effects of the amphetamines are more marked with the *l*-isomers, and come mainly through their α and $\beta 1$ and $\beta 2$ adrenergic agonist properties. Characteristic "fight or flight" effects of methamphetamine mediated through the α-receptors include mydriasis (pupillary dilation), bronchial muscle dilation, vasoconstriction, coronary dilatation, and bladder contraction. The heart rate accelerates, blood pressure rises, and blood glucose levels increase. The peripheral vasculature is constricted, increasing venous blood pressure, and cardiac output may be slowed. These effects can result in arrhythmia, regardless of the dose or blood concentration, placing patients with cardiovascular disease at high risk of heart attack. Other data suggests that cardiac effects may also be mediated indirectly by release of epinephrine into the circulation [87], and may contribute to changes in heart muscle following chronic use. Skin tremors may develop. In the male, ejaculation is delayed and intensity of orgasm is enhanced, which, coupled with the increase in libido associated with the use of this drug, gives it a popular reputation as a "sex drug". However, at higher doses and in more intense use patterns, users generally fail to achieve orgasm, and interest in sexual activity is consequently diminished.

The stereoselective nature of the peripheral actions of the amphetamines means that the effects and side effects experienced by the user will be determined to a great extent by the enantiomeric content of the drug ingested. Tolerance to peripheral effects including mydriasis may develop, although to what degree is extremely variable. The peripheral effects on the heart mean that the enantiomeric composition of the drug used may influence not only the quality of the drug experience for the user, but also the extent of the life-threatening pathophysiological effects. Certainly, in a law enforcement environment, care should be taken with restraints. "Hog tying", sitting on the subject's chest, or actions that will obstruct breathing should be avoided so as not to put additional strain on the cardiorespiratory system [104].

C. Route of Administration

Methamphetamine can be ingested via a variety of routes, and there is typically a progression following the start of use, from oral ingestion (often in gelatin capsules or now commonly in small wads of toilet tissue), or nasal insufflation, to intravenous use. Smoking of the drug achieved popularity in Asia and Hawaii in the 1980s, and was associated with "Ice", which was simply larger crystals of methamphetamine that were smoked in a pipe, much like crack cocaine. In spite of the media attention given this phenomenon, it never gained widespread popularity as a route of administration, and remains minor compared to the others discussed above. In Seattle, the routes of administration reported in the spring of 1998 were smoking (19%), intranasal use (36%), and IV use (44%) [15].

D. Patterns of Use

The motivation for abuse of methamphetamine is discussed later, but since the users' drug experience is determined largely by their pattern of use, and because of the limited degree to which the pharmacological literature has studied patterns of use, some discussion is merited here.

Methamphetamine has legitimate therapeutic use in the treatment of overeating disorders, where it can be used to control appetite, in narcolepsy, and in the treatment of Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD). Incentives for the mis-

use of the drug vary widely, and include its use by shift workers to combat fatigue or postpone sleep, by teen-age girls and others to suppress appetite during dieting (a frequent route of entry to drug use), and by students to help with studying or meeting deadlines, in addition to straightforward hedonistic, recreational use. Although the purpose for using will generally dictate the initial pattern of use, habituation to the CNS effects develops rapidly, and, if use continues, will generally deteriorate into bingeing as described below.

Single therapeutic dose (5–10 mg) administration of methamphetamine has received by far the greatest degree of study both from a pharmacokinetic and behavioral standpoint [13,14,20,45,46,86]. However, low-dose oral administration is not a common pattern of abuse, and in fact these subjects will most likely experience relatively little in the way of excitatory or euphorigenic effects, or other side effects that are likely to impair their performance.

The treatment community sees in their population (many of whom are referred from the criminal justice system), quite a different pattern — "binge" users, who can be classified as either low-intensity or high-intensity bingers (**Figure 1**). Methamphetamine binges typically take place over a period of two or more days, and will involve repeated administration of the drug at intervals of 1 to 5 h. The half-life of methamphetamine as discussed below is about 10 h, and highly elevated blood concentrations can be achieved following this pattern of use. The user is often involved in partying, sexual activity, shift work, or repetitive tasks requiring simple but focused attention, such as mechanical repair or tinkering, house cleaning, or long-distance driving. Obsessive-compulsive "sorting" behaviors are often reported. Bingeing is most frequently associated with intravenous administration. Once the drug supply is exhausted, or other imperatives prevail, the use of the drug ends, and the user starts to come down. The subject will frequently experience a phase known as "tweaking", (discussed below), which may last 6 to 18 h depending on the duration of the binge, followed by a crash characterized by lengthy non-restful sleep which may last a day or more, and then a return to apparent normalcy for a few days, during which a craving for the drug may appear, again depending on the degree of dependency developed in the subject.

Binges that extend beyond two days can be characterized as high-intensity binges. These may last for extended periods up to several weeks and may comprise shorter binges separated by brief periods (hours or days) of abstinence, but still contain all the phases discussed above, with a gradually deteriorating state of mind, frequently ending in a psychotic state.

In summary, the major negative effects of methamphetamine abuse appear to be largely a result of higher-dose, chronic, high-intensity, often intravenous, binge use. Little about the drug's most deleterious effects can therefore be inferred from the oral administration of clinical doses in a controlled environment over a period of a day or less. The body of literature on this topic should therefore be interpreted with caution when considering recreational patterns of use.

III. METABOLISM

Methamphetamine undergoes phase I metabolism by *N*-demethylation to amphetamine via the cytochrome P4502D6 isoenzyme system. Amphetamine itself is extensively metabolized to a variety of metabolites, including norephedrine and *p*-hydroxyamphetamine, both of which are pharmacologically active, and may be glucuronidated prior to excretion.

Several other drugs are metabolized to amphetamines. Benzphetamine (Didrex®), is metabolized to desmethylbenzphetamine, but also to *d*-methamphetamine and amphetamine, making enantiomeric resolution of limited value in determining the origin of the amphetamines in these cases [17,19]. Selegeline (Deprenyl®), a drug given in the treatment of Parkinson's disease, is unusual in that it is rapidly metabolized to *l*-amphetamine and *l*-methamphetamine, generally in equivalent amounts [95]. Famprofazone (Gewodin®), an analgesic with antipyretic properties, is metabolized to *d*- and *l*- methamphetamine and amphetamine, as well as 3-hydroxymethyl-propyphenazone. The latter metabolite is identified in urine only after enzymatic hydrolysis with beta-glucuronidase/arylsulphatase. The average amount of (–)-methamphetamine isomer excreted in the urine was found to be three times that of the (+)-isomer [80].

Figure 1. Schematic representation of a methamphetamine binge. The time axis is extremely variable and may represent from two days to several weeks. These phases are discussed in the text (after Stalcup [103]).

Fenethylline (Catpagon®), used in the treatment of attention deficit disorder, is metabolized to *d,l*-amphetamine [83]. Clobenzorex (Dinintel®), an anorectic, is metabolized to *d*-amphetamine, but use of the drug can be differentiated by measurement of the specific metabolite 4-hydroxyclobenzorex [7,107]. Other drugs metabolized to amphetamine include furfenorex [55], mefenorex [63], fenproprex [64], and prenylamine [89].

In summary, there are many drugs that metabolize to amphetamine or methamphetamine. Analysis of the specific enantiomer present, together with tests for the specific metabolite of the ingested drug and a consideration of the concentration of methamphetamine or amphetamine present, will all provide clues as to the origin of the measured drug. Nonetheless, irrespective of their origin, the effects associated with amphetamines in the blood, and consequently the brain, are significant and are discussed in detail later in this review.

IV. PHARMACOKINETICS

A. *l*-Methamphetamine and Use of Decongestant Inhalers

In the United States, *l*-methamphetamine (under the label *l*-desoxyephedrine) is the active constituent of the Vicks Inhaler decongestant, an over-the-counter product containing about 50 mg of drug. This isomer has about 25–33% of the CNS activity of its *d*-enantiomer. While the only way to completely eliminate this as a cause of a methamphetamine positive drug test result is a stereospecific test, the following considerations suggest that positive drug test results from use of this product are unlikely.

A single Vicks inhaler contains only 50 mg of *l*-methamphetamine. The recommended dosage is two puffs every 2 h for up to 7 h, with each puff dispensing about 21 ng. A subject following these recommendations would therefore receive around 300 ng of the drug [4]. This is an insufficient quantity to produce significant CNS effects, and would not result in a positive urine drug screen. However, very heavy use has resulted in urine methamphetamine concentrations of greater than 0.500 mg/L [18,35]. Anecdotal data from workplace drug testing programs suggests that the incidence of *l*-methamphetamine positives in workplace specimens is virtually unknown [22,98].

Abuse of *l*-desoxyephedrine products used to be quite common [38], but this usually involved opening the inhaler, extracting, and then injecting the drug. This practice is also followed for propylhexedrine [3], the active constituent of the Benzedrex® inhaler. The resulting product is sometimes called "peanut butter methamphetamine". Given the current availability of illicit *d*-methamphetamine and cocaine, the practice of inhaler abuse is now uncommon. The relative rates of metabolism of *d*- versus *l*-methamphetamine have been cursorily studied in some of the older literature. This literature, reviewed by Nagai and Kamiyama [76], suggests that both enantiomers show similar urinary excretion patterns; however, these authors' studies in rats have suggested that the *l*-isomer is more extensively transformed to *p*-hydroxymethamphetamine and *p*-hydroxyamphetamine than the *d*-isomer. They also note that humans have no chiral isomerization enzyme for *d*-methamphetamine.

B. *d*-Methamphetamine — Acute Dosing

1. Oral Dosing

The most comprehensive pharmacokinetic study of oral S(+)-methamphetamine (i.e., *d*-methamphetamine) was reported by Cook et al. [20]. The authors used deuterated drug for the first dose, followed by a sustained release preparation over 15 days, and concluded with a final deuterated dose. This allowed the evaluation of possible changes in metabolism or pharmacokinetics with chronic administration. With one exception (C_{max}, discussed below) there were no differences between the kinetics of the first and last dose. The authors consider, but discount, concerns that there might be differences in the metabolism of the isotopomers, and note that the elimination curves of the d0 and d3 isotopomers could be co-fit.

Following oral administration of deuterated *d*-methamphetamine hydrochloride doses of 0.125 or 0.250 mg/Kg (equivalent to 8.75 mg, or 17.5 mg respectively, in a 70 Kg (154 lb) subject), mean (n = 9) peak plasma methamphetamine concentrations of 0.020 mg/L and 0.039 mg/L, respectively, were achieved. The absorption half-life was 0.67 h. The time to peak was between 2.6 and 3.6 h (mean, 3.1 h), and the mean elimination half-life was 10.1 h, with a range of 6.4–15 h.

The maximum plasma concentrations of the amphetamine metabolite were observed at approximately 12 h after dosing, with mean concentrations of 0.0016 and 0.004 mg/L (1.6 and 4 ng/mL) after the low and high doses, respectively, i.e., approximately 15% of the concentration of the parent drug concentration present at that time.

Between 30% and 54% of the ingested dose was excreted unchanged in the urine, with a greater percentage being excreted unchanged at the lower dose. Between 10% and 23% of the dose was excreted as amphetamine. The pharmacokinetics were found to be essentially the same for the first dose (deuterated), as for the last dose (also deuterated) over a 15-day period, although follow-

ing the end of the higher-dose regimen, peak concentrations were slightly (but statistically significantly) higher than they were at the beginning. There was no apparent induction of metabolism or change in kinetics over the 15-day dosing period.

Concentrations of the drug in the saliva were approximately 7 times greater than in the plasma, but there was significant variability. The authors also note that methamphetamine kinetics can be markedly affected by abnormally acidic or alkaline urinary pH.

2. Smoking

The same authors reported on pharmacokinetic profiles in subjects following smoked and intravenous administration of *d*-methamphetamine in a second study [21]. When smoked, approximately 73% of a 30-mg dose was ingested as vapor, with the remainder of the drug being left in the glass pipe. The average dose ingested by the subjects was 22 mg of methamphetamine hydrochloride. Following smoking, the peak plasma concentration (mean, 0.047 mg/L) was achieved at around 2.5 h, but a plateau was sustained for an additional 2 h. The average elimination half-life was 11.1 h, with a range of 8.3–18.2 h.

Peak plasma amphetamine concentrations after smoking were quite low (around 0.004 mg/L) and again were achieved at around 12±2.3 h after dosing. Approximately 37% of the ingested dose was excreted in the urine as the parent drug, while 7% was excreted as amphetamine.

The kinetics of smoked methamphetamine are quite different in character from those of smoked cocaine, which is absorbed very rapidly with kinetics similar to that of IV administration. The kinetics of smoked methamphetamine more closely resemble that of oral administration. Cook et al. [21] attribute this to subjects swallowing some of the smoked dose, absorption of drug trapped or adsorbed on the mucosa, or the drug being retained in and slowly absorbed from the lungs. This is further compounded by the long half-life of the drug.

3. Intravenous Injection

The pharmacokinetic parameters following intravenous use were very similar to those seen following smoking, or oral use [21]. The peak methamphetamine concentration was achieved almost instantaneously, as would be expected, although there also appeared to be a rebound in concentrations within the first hour. The mean peak plasma concentration after a mean 12-mg IV dose was 0.097 mg/L. The mean elimination half-life was 12.2 h. Peak plasma amphetamine concentrations of around 0.004 mg/L were achieved after 17 h. Around 45% was excreted in the urine as the parent drug with around 7% excreted as amphetamine.

4. Summary

The smoked and intravenous routes of administration resulted in quite similar kinetics, with a slightly later peak following smoking. After oral ingestion, the peak was delayed by around 3 h. The mean elimination half-life appears to be independent of route of administration and in these subjects was around 10 h (oral), 11 h (smoking), or 12 h (IV injection). However, the ranges for half-life are broad (extremes of 6.4 and 18.2 h were found in this small study population), and, as noted throughout, are a reflection of variability in urinary pH. A volume of distribution of 3.5 L/Kg was noted. Furthermore, the data from the report on smoking/intravenous administration also suggested that methamphetamine kinetics might be dose-dependent with slower clearance at higher doses, due, at least in part, to a saturable excretion process in the kidney. This has important implications for the kinetics, and therefore the detection window, in high-dose, chronic, or binge use.

Because of the late peaking of amphetamine, and the low concentrations immediately following administration, a high methamphetamine-to-amphetamine ratio could be indicative of recent use, but as the authors note, multiple doses would confound this interpretation.

C. *d*-Methamphetamine — Chronic/High-Dose Dosing

In a study of the efficacy of treating narcolepsy with methamphetamine, Mitler et al. [75] gave 5, 10, 20, 40, or 60 mg single daily oral doses each morning over four days, and found the following mean morning (~2 h post-dose) and afternoon (8 h post-dose) serum drug concentrations (dose — mean a.m. conc. (mg/L), mean p.m. conc. (mg/L)): 5 mg — 0.011, 0.006; 10 mg — 0.023, 0.020; 20 mg — 0.050, 0.046; 40–60 mg — 0.117, 0.093.

Perez Reyes et al. [86] administered a daily 10 mg dose of a sustained release preparation of methamphetamine hydrochloride to six subjects for 15 days, with peak daily concentrations not exceeding 0.020 mg/L and dropping to 0.005 mg/L.

Anggard et al. [5] administered 20, 40, 80 or 160 mg of amphetamine intravenously to amphetamine-dependent, psychotic and non-psychotic patients. The corresponding serum amphetamine concentrations 1 h after administration were 0.056, 0.124, 0.260, and 0.595 mg/L. Other patients (n = 18) were administered 160 or 200 mg intravenously and achieved 1 h plasma concentrations of 0.365–0.600 mg/L (mean 0.423 mg/L).

Useful information can be obtained from examining the concentrations of the drug in the blood of subjects whose deaths were not a result of their drug use. This is

well illustrated as a "snapshot" of the concentrations in these subjects' blood at the time of their violent death. Bailey and Shaw [8] reported median blood methamphetamine and amphetamine concentrations in homicide victims (n = 25) of 0.490 mg/L (range: 0.030–7.100 mg/L) and 0.085 mg/L (range: not detected to 1.200 mg/L) respectively. Logan et al. [67] reported a median blood methamphetamine concentration of 0.550 mg/L (range: 0.030–9.300 mg/L) in 39 homicide victims. In fatally injured drivers, the same study reported mean blood methamphetamine concentrations of 0.350 mg/L (range: 0.050–2.600 mg/L).

It is clear that the typical concentrations in this abusing population represent rates of drug use far above those encountered in the laboratory pharmacokinetic studies discussed earlier. This has important implications for the performance and behavioral effects likely to result, and the reader is cautioned about inferring effects in the abusing population from those documented with low doses in laboratory subjects.

V. PHARMACODYNAMICS

A. Acute Administration — Therapeutic Dose

As noted in "Patterns of Use" above, the many negative effects of methamphetamine are likely sequelae to chronic, high-dose, or binge use, so the acute effects of low-dose administration are of limited relevance. Furthermore, there is no real therapeutic rationale for this type of short-duration dosing given the conditions indicated for legitimate prescription of this drug. Be that as it may, these acute effects are the easiest to study and therefore the most widely reported. They are discussed here to provide a context for the chronic effects discussed later.

At low doses, users report the following subjective effects: reduced appetite, increased alertness and energy, reduction of fatigue and drowsiness, general increase in psychomotor activity, and a general sense of well-being. They may also experience restlessness, dizziness, overstimulation, insomnia, mild confusion, and, in rare instances, panic or psychotic states (generally in individuals predisposed to schizophrenia).

In the smoking/intravenous study abstracted above [20], peak subjective effects were achieved 18 min after the start of smoking, or 17 min after intravenous injection. When smoked, the peak subjective effects preceded the peak plasma concentration by about 2–3 h, providing evidence for the development of acute tolerance.

Effects from smoking or intravenous administration included an increase in mean heart rate (to 97 bpm (smoking) or 105 bpm (IV)), stroke volume, and cardiac output for the first 30 min following administration [87]. Blood pressure (systolic and diasystolic) showed a marked increase within the first 30 min, and a tendency toward increased levels throughout the subsequent 3 h. This is correlated with an initial drop in total peripheral resistance, which, particularly in the case of IV use, tended to rebound to elevated levels over the ensuing 3 h. After smoking 40 mg, subjects reported hypomanic symptoms for about 2 h, intense craving for further doses, difficulty in concentrating, memory lapses, and insomnia. These changes in vital signs all have important consequences for the Drug Evaluation and Classification Program (DECP, sometimes DRE) examination discussed later.

B. Chronic Administration — Therapeutic Dose

This type of dosing pattern is characteristic of therapeutic use in the treatment of narcolepsy, eating disorders, and attention deficit (ADD) and attention deficit hyperactivity disorders (ADHD). In these situations, the recommended dose is 5- to 10-mg doses with occasionally as much as 60 mg being given. Mitler [75] reported improvements in mean sleep latency time, and also improvement in a driving simulator obstacle course, which is discussed later. Under these dosage conditions, he found no significant increase in blood pressure, pulse, or respiration rate, although these measurements were made each day some hours after dosing. Side effects appeared in a dose-dependent manner and included loss of appetite, insomnia, headache, nervousness, and motor restlessness. There was no reported change in mood or libido.

Perez Reyes' study [86] did find some tolerance to the tachycardic effects of the drug over a 15-day period, but not to the elimination half-life, subjective high, or blood pressure.

C. Abuse — High-Dose and Chronic Administration

For obvious reasons this is the most difficult kind of pattern to study in a laboratory setting due to ethical and informed consent issues. A report by Bell [9] of work conducted between 1959 and 1967 describes a series of 14 psychotic patients with a history of methamphetamine use who were administered high doses of methamphetamine in an effort to reproduce the psychosis. These subjects, who reported maximum daily dosages as high as 1000 mg, received up to 640 mg of drug intravenously over about 1 h, until symptoms of psychosis appeared. The psychosis lasted 1–2 days in 9 patients, 5 days in 2, and intermittently in 1 patient for 26 days who, it later was discovered, was surreptitiously taking more of the drug!

Typical constellations of symptoms are described by several authors [28,61,62,101] and are summarized here.

At higher doses, particularly following intravenous use, users typically report intense exhilaration and euphoria, extreme wakefulness, rapid flow of ideas, feelings of increased physical and mental capacity, garrulousness, talkativeness, and rapid speech. Elevated self-esteem and intense sexual arousal are also common. Thought patterns tend to be rapid and of a decisive nature. These effects are perceived as positive and generally encourage repeated administration, producing a binge-type use pattern. As the binge progresses, the drug is repeatedly administered every few hours over a period of hours or days. Often as early as the second day, the subject enters a phase known as "tweaking". During this phase, euphoria is gradually replaced with mounting anxiety, inability to concentrate, and delusions. The user is anxious, irritable, short-tempered, and introspective. Pseudohallucinations can occur, and paranoia sets in. These unpleasant effects can be temporarily eliminated by re-administration of the drug, again reinforcing use, but the highs become less intense and the lows become lower as the binge proceeds. Eventually the user becomes so tired and fatigued that they may "nod off" to sleep and then start awake, reporting dysphoria, fatigue, anergia, anhedonia, and exhaustion. At this point drug administration will cease, and the user enters the "crash" phase. This period of restless, light sleep can last for a day or more, during which there is a compulsion to sleep or an inability to maintain consciousness. The longer the duration of the binge, the greater the likelihood that a psychosis, characterized by true hallucinations and delusions, will develop. This condition is often indistinguishable from a schizophreniform psychosis, and can only be differentiated in that it will resolve over time as the drug is cleared from the body and homeostasis restores the neurochemical balance. As will be seen, the symptomatology for acute high-dose use is very similar to that reported for chronic use, which is invariably high-dose. Gawin and Kleber [39] have described and characterized abstinence symptomatology in cocaine users, and that syndrome contains many features similar to those encountered in methamphetamine withdrawal.

Anggard et al. [5] measured amphetamine concentrations in serum of psychotic patients admitted to hospital and found concentrations of 0.161–0.530 mg/L within the first day of admission. Subjects were displaying lack of concentration, paranoid delusions, hallucinatory behavior, and disorganization of thoughts, but importantly there was no correlation between the plasma amphetamine concentration and the degree of psychosis.

Smith and Fischer [102] reported symptomatology in a group of 310 patients reporting to a treatment facility with acute high-dose methamphetamine toxicity. Among the more prominent conditions reported were acute anxiety (28%), amphetamine psychosis (18%), malnutrition (12%), and exhaustion syndrome (9%). More recently, Derlet et al. [25] reported symptomatology in 127 cases of amphetamine toxicity in Sacramento. The findings were similar with 57% reporting altered mental status, including agitation, suicidal ideation, hallucinations, confusion, and despondent affect. Only 10% of the patients had been found unresponsive. Richards et al. [90] have reported blunt trauma as the most frequent cause of admission (33%) to an emergency room in methamphetamine intoxicated patients, followed by an altered level of consciousness (23%), including acute agitation, hallucinations, (e.g., "skin bugs"), tonic-clonic seizures, and fainting. Similar patterns are reported by Chan et al. [16] in a group of eight patients admitted to an emergency room in Taiwan. Three patients were in a coma, and three of the remaining five reported hallucinations, agitation, confusion, and muscular twitching.

In a review of symptomatology in a group of nine patients reporting with amphetamine psychosis, Hall et al. [43] reported among the more frequent findings, ideas of reference, increased motor behavior, paranoid ideation, paranoid delusions of influence, visual illusions in peripheral field, lability of mood, and increased sex drive. Many of the subjects were unable to separate their psychotic experiences from reality after the psychosis had resolved. A similar description is provided for other drugs, in addition to amphetamine, by Hurlbut [49].

The treatment of methamphetamine abusers with acute toxicity as described elsewhere has been addressed by Richards and co-workers [91,92]. They evaluated droperidol and lorazepam for the chemical restraint of agitated, combative patients, most of whom had been using methamphetamine. The subjects were typically very agitated, combative, violent, and out of control. Although both drugs effectively sedated the patients, the authors recommend the use of droperidol because of its longer half-life.

D. Summary

Clearly the most important effects with respect to psychomotor impairment and behavioral effects are found outside of the normal patterns of low-dose, therapeutic use, and therefore the real value of most of these studies is in helping us differentiate abuse from therapeutic use. It is evident that normal therapeutic dosing is around 10 mg/day, and does not exceed 60 mg/day, generally by mouth, usually in divided doses. Even this high dose will result in peak methamphetamine concentrations of 0.020 mg/L or less. If a sustained release preparation is used, concentrations will typically be lower. More common are doses of

5 mg or 10 mg, resulting in peak concentrations of 0.005 to 0.010 mg/L. Negative psychomotor effects at these doses can occur, but are uncommon. Conversely, there is excellent evidence that performance in some motor skills is restored in fatigued subjects, and plentiful, if less consistent, evidence that performance can be improved in non-fatigued subjects.

The most profoundly impairing effects result from high-dose use, which in many cases may be distinguished based on blood concentrations. As noted above, concentrations of methamphetamine exceeding 0.020 mg/L can reasonably be assumed to result from abuse, and effects of the drug on self-perception, critical judgment, attention, risk-taking, mood, and motor restlessness may all contribute toward a deterioration in safe driving. However, an important exception to this ability to distinguish use from abuse based on blood concentrations is in the impairment suffered during "tweaking" or withdrawal. During this period, which can last for days following the time of last use, the blood drug concentration will decline to subtherapeutic concentrations, while the potential for withdrawal-induced impairment discussed above (irritability, anxiety, paranoia, delusions, hallucinations, and most importantly, fatigue) is at its height. Therefore, low (<0.020 mg/L) concentrations do not exclude the possibility of impairment. This is discussed in more detail when specific effects on driving are considered below.

VI. FORENSIC ISSUES

A. Methamphetamine and Violence

In a review of deaths associated with methamphetamine use [67], one startling factor was the marked incidence of homicidal or suicidal violence. Eighteen of the deaths were suicides, and the causes of the other deaths were gunshot wound (11 cases), CO poisoning (3 cases), hanging (2 cases), and falls (2 cases). In most cases it was not possible to determine precisely the factors that led to the decision to commit suicide. However, methamphetamine use can contribute to suicidal behavior as a result of economic, social, and psychological pressures, as well as the impaired judgment and lack of critical thought associated with both stimulant impairment and abstinence syndrome.

In this population [67] there were 40 homicides where the subject tested positive for methamphetamine, with the cause of death being gunshot wound (31 cases), stabbing (7 cases), or strangulation (1 case). The blood methamphetamine concentrations in homicide victims ranged from less than 0.03 mg/L to 9.30 mg/L (median 0.550 mg/L). By way of comparison, Logan et al. [69] have reported survival of a subject (following medical intervention) with a blood methamphetamine concentration of 9.50 mg/L, showing that extremely high methamphetamine concentrations are not always lethal. Similarly, in this series, in those cases with higher methamphetamine concentrations, the cause of death was invariably gunshot wound. The presence of these high levels in ambulatory individuals illustrates one of the difficulties in designating a presumptive "lethal" level or range for the drug, or determining cause of death solely from toxicology results. Eighty-three percent of the homicide victims had blood concentrations of methamphetamine less than 1.0 mg/L. These are likely representative of the levels routinely achieved in live methamphetamine abusers.

Over the same period of time, for deaths in Washington State in which the victim tested positive for morphine, only 4% were homicide victims and 6% were suicides. By comparison, in decedents testing positive for cocaine use, another stimulant, 18% were homicide victims and 9% were suicides. This compares to 27% homicides and 14% suicides testing positive for methamphetamine. Much anecdotal evidence has suggested an association between violence and stimulant use in general, and methamphetamine use in particular. Logan [66] reported that violent behavior in subjects arrested for driving under the influence (DUI) who later tested positive for methamphetamine was more consistently noted in individuals with blood concentrations greater than 1 mg/L.

There is also a suggestion in both the sociological and criminological literature that users of illicit drugs, including the amphetamines, are more prone to victimization than the general population. Kingery et al. [58] reported that adolescent drug users fought more, took more risks that predisposed them to assault, and were assaulted more often than non-drug users. Drug use by both the victim (14%) and the victim's dating partner (27%) was reported in a study of violent dating incidents [12]. Drug use was also reported as being common in both victims and perpetrators of domestic violence [99]. Among the reasons cited for this are a combination of the following: low self-esteem, anxiety, and depression leading to drug use; involvement in a culture in which possession of weapons is common; and the development in co-users of paranoia, violent tendencies, impaired judgment, and poor impulse control. These factors can all engender an atmosphere in which minor disagreements or misunderstandings can quickly escalate to homicidal violence [27]. Although there is much anecdotal evidence, there is no objective data clearly demonstrating the causal link between violent behavior and methamphetamine use/blood concentration. Stimulant-related violence is also discussed by many other authors [49,61,74,99,101].

B. Methamphetamine Combined with Alcohol and Other Drugs

Methamphetamine is frequently combined with other drugs, including alcohol [109], marijuana, narcotic analgesics, other stimulants, and depressants [60] and it is often difficult to separate effects of one drug from another. The combinations — "goofballs" (amphetamines and barbiturates), or "speedballs" and "bombitas" (amphetamines or cocaine and heroin) — are taken to provide a "relaxed high" or to offset some of the agitation and irritability experienced during high-dose amphetamine use. Depressants, including alcohol, are also used to help during tweaking or withdrawal to assist with sleep. Marijuana may also be used in this phase, or simply to customize the amphetamine experience.

A concern in assessing potential effect of methamphetamine is whether the co-administration of stimulants and depressants would tend to cancel out the effects of either drug. A few studies have examined the co-administration of amphetamines with other drugs in man.

In evaluating the combined effects of alcohol and methamphetamine, Forney [37] reviewed work by Rutenfrantz and Jansen [96], which suggested that low-dose methamphetamine (9 mg, IV) partially reversed the effects of low doses of alcohol in subjects in a driving simulator, yet their results were based on only two subjects, have not been replicated, and in fact have been contradicted by other researchers. In a study of alcohol (BAC ~0.05g/100mL) and amphetamine (dose: 0.2 mg/Kg (14 mg/70 Kg)) effects on mood and volition measured by betting in a card game [53], alcohol produced a greater degree of risk-taking. Amphetamine alone, or in combination with alcohol at this dose, did not appear to affect risk-taking.

In a blinded crossover design study [33] subjects were administered placebo, amphetamine alone, marijuana alone, or marijuana and amphetamine. However, the amphetamine dose was oral, acute, and low (10 mg), and subjects could distinguish, with reliability, the amphetamine from the placebo. Subjects still reported a more intense high from the drug combination than from either drug alone. The effects appeared to be additive. Heart rate increased acutely with the smoking of marijuana, but the increase was sustained longer when both drugs were co-ingested. Psychomotor changes (especially slowing of reaction time) appeared to be most readily attributable to the marijuana use, and there was no evidence that the amphetamine restored the performance lost.

Wilson et al. [108] co-administered a 15-mg dose of amphetamine with or without alcohol and had subjects perform a variety of psychophysical tests. The results indicated that each drug modifies the effects of the other. Amphetamine produced no improvement of ethanol-impaired performance in most tests, although in some simple repetitive tasks (serial addition, coding, and trail-making), it did. The results indicated that when both drugs were present together, the effects could not be predicted on the basis of depressant versus stimulant competition.

Mendelson et al. [72] reported that methamphetamine (30 mg IV) did not change ethanol (BAC ~0.08g/100mL) intoxication self-ratings, although heart rate increase was greater and more sustained following administration of the combination.

Newman and Newman [82] reported that neither caffeine nor amphetamine (15 mg) were effective in restoring ethanol-induced performance impairment in tests of balance, steadiness, and fusion.

In summary, there is no reason to believe that on a neurophysiological level the stimulant effects of amphetamine use would be negated by the ingestion of a depressant, or vice versa, and this is borne out by the studies reviewed. Combining drugs that individually have a complex effect on mood, sensorium, judgment, risk-taking, and values inevitably complicates things even further, making these executive operations less predictable and more subject to error. These studies suggest that even at the low doses of amphetamine used, the impairing effects are generally additive to those of the depressant, but, as in the case of fatigue, some performance decrement in simple repetitive tasks may be improved.

C. Military Use and Effects on Counteracting Fatigue

As early as 1966, it was recognized that the performance enhancement resulting from amphetamine use was generally significant in restoring performance in fatigued subjects, rather than producing performance above baseline in normal subjects [65]. The effects of fatigue are of great concern to the military, particularly in a combat setting. Newhouse et al. [81] reported on the efficacy of *d*-amphetamine (10 or 20 mg) on restoring baseline performance in subjects deprived of sleep for 48 h, and found a dose-related level of improvement. The use of amphetamines by the military is an issue that deserves attention, since superficially it may appear at odds with arguments expressed here that abuse of methamphetamine would inevitably produce impairment.

Ever since its invention in 1919, the potential benefits from this drug in a military setting have been appreciated. It was used by both the Allied and Axis powers during the Second World War to allow prolonged forced marches, and to keep troops awake and alert in protracted combat. Military use of the drug to counteract fatigue has contin-

ued through to the present day. In Operations Desert Storm and Desert Shield during the Gulf War, pilots were issued "GO" pills (*d*-amphetamine, 5 mg) [32]. They were limited to the use of one pill every 4 h to combat fatigue resulting from sustained flying operations (duty days of greater than 16 h and crew rest periods of less than 6 h), and time zone changes. As many as two thirds of the pilots flying there used the pills, and the rating of the effects was almost uniformly positive, many stating that they felt it made for safer flying operations. However, in contrast to typical recreational patterns of use, the drug was administered orally, in small divided doses, under the direction of a flight surgeon.

Caldwell et al. [14] demonstrated the ability of amphetamine (30 mg in divided 10-mg doses at 4-h intervals) to sustain helicopter pilot performance in a flight simulator during periods of sleep deprivation (over 48 h without sleep). There was reduced slow wave EEG activity, improved alertness, and better self-ratings of fatigue and vigor. These results were generally validated by Caldwell and Caldwell [13] in actual helicopter flight, although the drug's effects were less significant, and did not become significant until after 24 h of sleep deprivation.

Fatigue is generally recognized as a major contributor to driving impairment [11,105], so the notion that amphetamines could be used to counteract this effect in fatigued drivers is not so farfetched. Nevertheless, the doses of amphetamines typically used in a recreational situation are well beyond what has been validated as being effective in reversing these effects. Also, as discussed later, fatigue induced as a result of amphetamine abuse cannot be reversed by further administration of the drug.

In summary, when a subject is fatigued, performance in simple psychomotor tests of short duration is barely effected, but performance impairment becomes marked when sustained effort is required, or when the task is more complex. The administration of 5- to 10-mg oral doses of amphetamine at 4-h intervals has been shown to be effective in restoring performance for periods up to 40 h. The effects of more prolonged or frequent administration, intravenous or smoked routes of administration, or the use of higher doses has not been investigated.

D. Methamphetamine and Driving

There are at least three ways to evaluate the potential impact of methamphetamine on driving. The first is by examining the physiological and psychological effects of low-dose therapeutic administration through high-intensity binge abuse, and drawing conclusions about the potential impact of the typical signs and symptoms on a complex psychomotor task like driving. The second approach is to examine case reports or epidemiology of drivers involved in traffic accidents or impaired driving arrests. A third approach is to examine laboratory reports of performance in driving simulators or laboratory tests of psychomotor performance following methamphetamine administration. Considered together, this information should give a picture of the impact of methamphetamine on driving, including information about any causative link.

1. Empirical Considerations

Starting with the first and most empirical approach, methamphetamine is a stimulant drug, which at low oral doses is effective in offsetting the consequences of fatigue on psychomotor performance. The effects reported at this level of dosing are improved alertness, improvement in reaction time, elevation of mood, reduction of sleepiness, suppression of appetite, pupillary dilation, and some transient increase in heart rate and blood pressure. Occasionally headaches, insomnia, light sensitivity, and irritability are reported as side effects. Based on these considerations, one would not expect widespread adverse effects on driving from this pattern of use. Furthermore, it should be recognized that in cases where a driver is fatigued from loss of sleep (24–36 h without any sleep), the drug might restore some of the fatigue-induced impairment, and thus restore performance to baseline level.

Nevertheless, at elevated doses or after prolonged administration of the drug, and especially after intravenous administration, the effects are quite different. During acute intoxication the CNS effects are intense, distracting, and overwhelming, including, as discussed earlier, exhilaration and euphoria, rapid flow of ideas, feelings of great physical strength and mental capacity, excitation, panic, and sexual arousal, often referred to as the "upside". Less frequently, hallucinations, delusions, perceptual distortions, and assaultive behavior also occur. Most of these effects can reasonably be expected to contribute at a minimum to a decline in concentration, inability to divide attention, and errors in judgment and perception. Perhaps more importantly, as the binge progresses, and the tweaking, and crash or withdrawal phases (often referred to as the "downside") become established, the symptomatology becomes quite different. The user becomes preoccupied with their thoughts and behavior, the euphoria is replaced with agitation, concentration becomes difficult, and "pseudohallucinations" appear (these are frightening visual images that the user knows to be unreal, or can be persuaded are unreal). The subject often becomes confused, irritable, paranoid, and increasingly fatigued. Progressively, the presentation becomes one of CNS depression, progressing to periods of uncontrollable sleepiness

and "microsleeps", lasting a few seconds to minutes from which the user starts with disorientation and unease before finally falling into a troubled, restless, sleep. The extensive literature on driving impairment from CNS depressants, particularly alcohol, demonstrates a clear link between their effects and driving impairment, suggesting that this phase of methamphetamine intoxication presents real risks for psychomotor impairment and corresponding risks to driving performance.

2. Epidemiology

The second approach is to consider epidemiological reports, such as rates of amphetamine use among fatally injured drivers, or accident rates among drug users.

Smart et al. [100] reported on rates of accident involvement among a variety of groups of drug abusers, and found that the group of amphetamine users were the most likely to have an increased accident rate over the driving population in general. This study is unusual in that it contains a control group.

The following literature review is taken in part from Logan [66]. Several studies of driver populations have included tests for amphetamines and show a significant incidence of their use. Lund et al. [70] studied drug use in truck drivers on a major U.S. transcontinental highway and found methamphetamine in 2% of those drivers voluntarily tested. However, 12% of drivers contacted declined to participate. Crouch et al. [24] reported on the prevalence of drug use in fatally injured truck drivers and found amphetamine or methamphetamine in 7% of cases (*see* [79]). Comparing Lund's data to that of Crouch suggests that methamphetamine use is overrepresented in fatally injured truck drivers. This would support a causal relationship between methamphetamine use and increased risk of fatal accident involvement, but the refusal rate in Lund's study makes this comparison less than conclusive.

Kirby et al. [59] reported drug use in traffic accident victims admitted to a level one trauma center in 1988 and found an incidence of amphetamine use of 2%. Robb et al. [94] reported on drug use in drivers in New Mexico arrested under suspicion of driving under the influence of drugs (DUID) and found 1.7% positive for non-cocaine phenethylamine stimulants. Logan and Schwilke [68] reported 1.8% of fatally injured drivers in Washington State testing positive for methamphetamine. Unfortunately, there is no corresponding control group in any of these studies to permit evaluation of the relative prevalence of amphetamine use in impaired drivers as opposed to the general driving population. In addition, since many of these studies tested only urine, blood drug concentration data is not available. This is regrettable since such information would be useful in establishing any link between the concentration of the drug and its role in the cause of the accident.

In 1992, the National Highway Traffic Safety Administration (NHTSA) published a review of drug use in fatally injured drivers [77]. The most frequent type of accident among drivers testing positive for amphetamines was a "non-collision" or drive-off-the-road-type accident (50%, compared to 32% in the drug-free control group). A total of 83.3% of the amphetamine-positive drivers were deemed responsible for the accident, compared to 67.7% in the drug-free control group, and 93.9% in the group with blood alcohol greater than 0.09 g/100 mL.

In summary, there is some evidence from these studies that amphetamine use is prevalent in certain driver populations, but it remains difficult on this basis alone to infer a causal link due to the absence of control data. Nevertheless, studies documenting rates of methamphetamine use in driving populations do allow identification of trends and comparisons of drug-use patterns between groups and jurisdictions.

3. Laboratory Studies and Other Reports

A third source of information is a review of the literature on amphetamines and driving performance. Ferrara et al. [34] conducted an extensive review of literature on laboratory studies involving performance following administration of psychostimulants. Approximately 5% reported impairment, 32% reported no effects, and 38% reported improvement, but Ferrara did not consider dose in this evaluation.

Evans et al. [33] had subjects rate whether their driving was impaired after a 10 mg/70Kg dose of *d*-amphetamine. Of 11 subjects, one subject in the placebo group, versus three in the amphetamine group reported impairment (compared to 7 of 11 in the marijuana group, and 8 of 11 in the combined amphetamine/marijuana group). Mitler et al. [75], in studying the effects of methamphetamine on narcoleptic patients and controls, included 30-min sessions on a simple computer-based "driving simulator". Methamphetamine displayed a dose-dependent improvement in performance in narcoleptics up to 60 mg, and in controls up to 10 mg.

Hurst [50] tentatively concluded that a 10-mg oral dose of amphetamine increased risk-taking. This finding was supported by further work by Hurst et al. [54] evaluating effects of amphetamine (14 mg/70 Kg) on judgment and decision-making. These researchers found that both decisions to accept risk and self-appraisals of performance were increased. In later work [52], he failed to measure any increased risk taking in another gambling construct with the same dose. Although tentative, and contradictory in places, and based on low-dose adminis-

tration, these findings demonstrate at least the potential for effects on decision-making and risk-taking that could impact driving behavior. Subsequent to this work, Hurst had reviewed the issue of amphetamines and driving on two separate occasions [51,52]. He notes [51] that as discussed above, there is little direct evidence that normal therapeutic doses affect driving, and downplays the risk-taking aspects in his earlier studies due to their mild effects.

Ritalin (methylphenidate) is another stimulant drug used to treat adults with attention deficit hyperactivity disorder (ADHD), and the effects of this medication on their driving have been assessed [23]. These researchers found that ADHD adults had a higher accident rate, more moving violations, and poorer simulator driving performance than non-ADHD controls. Their performance under Ritalin treatment demonstrably improved their driving over the unmedicated condition. Other researchers have shown similar findings [56].

Ellinwood and Nikaido [30] further explored the issue of stimulant-induced impairment, looking in detail at the issue of the effects of the downside of these drugs, including the amphetamines. They present a general dose-dependent model for stimulant impairment, considering arousal, hyperarousal and withdrawal phases, which was developed further by Logan [66], who reported symptomatology from a series of 28 drug-impaired driving cases, and used the data to produce a more detailed model for methamphetamine-impaired driving based on Ellinwood and Nikaido's general model (*see* **Figure 2**). That review concluded that while neither the degree of impairment nor the phase of intoxication could be predicted from the blood methamphetamine concentration, abuse could be distinguished from therapeutic use when the concentration was greater than 0.200 mg/L. Conversely, however, lower concentrations do not exclude recreational use beyond the impairment threshold since the subject may be on the "downside", or withdrawing. In the majority of cases reviewed, the pattern of driving (typically one-car, drive-off-the-road-type accidents) was highly suggestive of withdrawal-induced impairment, and several of the drivers reported "falling asleep". Other driving patterns included high-speed and high-risk driving. The vast majority of subjects also demonstrated behavioral signs suggestive of high-dose or binge use.

In support of this, Logan et al. [67] reviewed 146 deaths involving methamphetamine, including 17 fatally injured drivers. In this group, 14 of the 17 fatalities resulted from drive-off-the-road-type accidents, again strongly suggesting withdrawal-induced impairment, and consistent with the earlier report.

Figure 2. Hysteresis plot showing examples of effects which can impact driving performance with respect to blood methamphetamine concentration (mg/L) in two illustrative cases. The figure shows examples of withdrawal effects from (a) low-dose, and (b) high-dose drug use. (Reproduced with permission from *J Forensic Sci* [66] — Copyright ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428.)

4. Methamphetamine and the DRE Evaluation

Methamphetamine falls into the stimulant category in the drug recognition expert (DRE) scheme. Physiological signs, which may help the DRE officer correctly identify stimulant use, include increased pulse and blood pressure, dilated pupils, increased muscle tone, muscle tremors or tics, restlessness, agitation, scratching, and repetitive, rapid speech. During the interview the subject may appear nervous, paranoid, may have delusions, may hallucinate, and may give confused responses to simple questions. They may also become violent, particularly if startled, or frightened, such as may happen when taken into the dark room for the pupil exam, so officers should be advised to take extreme caution. Pupillary dilation can make them extremely sensitive to light, so care should be taken with the penlight or flashlight.

A number of DRE officers have reported evaluating subjects on the "downside" of methamphetamine use, where the symptoms may be subtly different. As the person moves from the "tweaking" phase to the "crash", their vital signs can become depressed, heart rate and blood pressure may be normal to low, pupil size has been reported to be in the low end of the normal range (~2–3 mm), and they become drowsy and sleepy, and may "nod off". This symptomatology includes many of the signs associated with narcotic analgesics, or depressant use, such as depressed pulse and blood pressure, so care should be taken with the evaluation. The major distinguishing features are the fact that the subject's pupil, although small, will still react to light, which the narcotic analgesic user's pupil will not. Even when they are nodding off, the subject's behavior and state of mind during the period when they are awake are generally more alert than in the narcotic analgesics user, and some behavioral manifestations of stimulant intoxication will generally be present.

Heishmann et al. [45,46] presented data on subjects who had been administered oral doses of 0, 12.5, or 25 mg of amphetamine, and were then subjected to a DRE evaluation 140 min later. These doses are extremely conservative in terms of normal recreational doses, which range into the 100s of mg to g, administered over many hours or days. The authors found that with the low dose (12.5 mg) only 7 of the 18 subjects displayed any signs of intoxication, meaning that in a field or arrest setting, the remaining 11 would not have been arrested or subjected to the complete DRE exam. Furthermore, of the 7 deemed impaired, only 2 were correctly identified as being under the influence of a stimulant. The high-dose subjects did not test much better, with 8 of 18 being deemed impaired, and only 3 of the 8 correctly identified as being under the influence of a stimulant. Most often these subjects were thought to be under the influence of marijuana, based principally on the elevated pulse and blood pressure, and dilated pupils, but absent the agitation and excitation associated with stimulant use. Because of the limitations on dose in this study, it cannot be reasonably used to assess the efficacy of the DRE evaluation in amphetamine-impaired subjects.

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