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Cause and Manner of Death in Fatalities Involving Methamphetamine

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ABSTRACT: We reviewed a series of deaths in which methamphetamine was detected in the decedent's blood. Analysis of postmortem whole blood was performed by gas chromatography/mass spectrometry with a limit of quantitation of 0.05 mg/L. Methamphetamine was detected in 146 cases; 52 were drug caused, i.e., a death in which the direct toxic effects of the drug caused or contributed to the death, 92 were classified as drug related, i.e., a death in which the drug was demonstrated in the blood, but did not directly cause death. A large proportion of the deaths resulted from homicidal (27%) or suicidal (15%) violence. An examination of methamphetamine concentrations in drug related deaths ($n = 92$), suggests that the range of concentrations in the recreational abusing population is substantial (0.05–9.30 mg/L) but with a median concentration of 0.42 mg/L, and with 90% of that population having concentrations less than 2.20 mg/L. There was substantial overlap in methamphetamine concentration between drug related deaths and drug caused deaths, although the highest concentrations were seen in the unintentional (accidental or undetermined) drug caused deaths. Methamphetamine related traffic deaths ($n = 17$) showed patterns of driving behavior consistent with reports elsewhere, and showed blood methamphetamine concentrations ranging from 0.05–2.60 mg/L (median 0.35 mg/L).

The data show that most methamphetamine deaths occur with blood concentrations greater than 0.5 mg/L, but can occur with levels as low as 0.05 mg/L, though usually in conjunction with other drugs or significant natural disease. Neither apparently toxic nor therapeutic concentrations should be used in isolation to establish conclusively whether a death was caused by methamphetamine; proper classification of deaths involving methamphetamine requires complete death investigation, including investigation of the scene and circumstances of death, and a complete autopsy.

KEYWORDS: forensic science, methamphetamine, death, violence

Methamphetamine (also known as amp, meth, crystal, crank, speed, ice, whizz, etc.) is a dopaminergic central nervous system stimulant. It acts both by promoting release of norepinephrine and inhibiting its re-uptake, and is a potent blocker of dopamine reuptake (1). It is easily synthesized from readily available precursors, and has been a popular drug of abuse in the United States since the 1940s (2,3). The drug is commonly administered by insufflation, ingestion, injection, or by smoking. Patterns of abuse vary from occasional periodic use, to runs or sprees, where the user will ingest large quantities of the drug, usually by intravenous injection, over a period of several days (4,5). During the run the user will be in a hyperactive, manic, stimulated, or euphoric state, characterized by high energy, rapid speech and rapid flight of ideas, depressed appetite, and often by increased libido, agitation, paranoia, apprehensiveness, confusion, and delusions. Seizures, cardiorespiratory depression and death can occur (6). A progressively developing psychotic state, symptomatically indistinguishable from schizophrenia, commonly develops after prolonged use, and while it can result from oral administration, it is more frequently associated with intravenous administration (4,5,7–10). Violent behavior, usually in response to paranoid delusions, frequently occurs, often without a fully developed psychosis. A run of methamphetamine use is followed by a period of marked withdrawal, during which the subject experiences extreme fatigue, exhaustion, disorganization, hypersomnolence, depression and drug craving (4,11). Long term methamphetamine use can have serious health consequences (12) including malnutrition, exhaustion, and infection problems, the latter generally associated with poor needle hygiene in intravenous drug users. In addition, the propensity for paranoia associated violence after prolonged use may involve the user in life threatening situations (5,13,14).

There are indications from epidemiological data and the recent experience of the authors, law enforcement and treatment communities, that the illicit use of methamphetamine has been increasing in Washington State over the last three years. Nationally, the Drug Abuse Warning Network (DAWN) reported an increase in emergency room mentions of methamphetamine of 34% over the same period in 1994 (15). Data reported to DAWN from Harborview Medical Center, Seattle, the largest public hospital in Washington state, showed an increase in emergency room mentions of amphetamines from 7 in the first half of 1991, to 163 in the same period in 1995. Methamphetamine has also emerged as a major contributor to drug impaired driving arrests and crashes in the state over the same period (16).

In an effort to reach a better understanding of the interpretability of blood methamphetamine concentrations in cases of suspected drug caused or related death, we reviewed all deaths occurring during the period January 1993 through December 1995 inclusive, in which methamphetamine was detected in the decedent's blood. The cause and manner of death, and complete toxicology results were evaluated to determine those factors which might assist in the interpretation of future methamphetamine related deaths.

Methods

Deaths falling under the jurisdiction of the county coroners and medical examiners in Washington state were investigated and

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where appropriate, samples of blood from intact peripheral vessels (and when available, urine) were collected and submitted to the Washington State Toxicology Laboratory for analysis for basic and alkaloidal drugs, weakly acidic and neutral drugs, and low molecular weight volatiles including ethanol. Methods are as described elsewhere (17,18). Drug screening for amphetamines in urine was performed using enzyme multiplied immunoassay with a monoclonal antibody (EMIT DAU, Behring, Palo Alto, CA). Drug testing in blood was performed using gas chromatography with nitrogen phosphorus or flame ionization detection, with confirmation by gas chromatography/mass spectrometry (GCMS). This testing routinely detects the presence of amphetamine and methamphetamine at concentrations above 0.05 mg/L in blood, and above 300 ng/mL in urine.

For all cases in which methamphetamine was detected in the decedent's blood, the death certificates and toxicology reports were reviewed, and in approximately 40% of the cases, investigative and autopsy reports were available and reviewed. Each case was categorized as either drug caused or drug related. A drug caused death was defined as a death in which the direct toxic effects of the drug caused or contributed to death. A drug related death was considered to be a death in which the drug was demonstrated in the blood, but did not directly cause death; in drug-related deaths, effects of the drug may have been responsible for the incident which resulted in the injuries considered to have caused the death, such as traffic fatalities. Drug caused deaths were sub-classified as methamphetamine-only overdoses, overdoses of methamphetamine and other drugs, and methamphetamine present with co-existent significant underlying natural disease.

Results and Discussion

Methamphetamine was detected in 146 cases, and data on the subjects' gender, age, pathology and cause and manner of death were collated. There was no indication from the histories in any of these cases that the methamphetamine detected resulted from use of over the counter 1-methamphetamine (Vicks inhaler), or selegeline (deprenyl), an antiparkinson medication which is metabolized to methamphetamine, or from legitimate prescription of methamphetamine itself. The need for this differentiation has been evaluated in an earlier report (16). The assumption in all these cases, therefore, is that the methamphetamine detected was the d-isomer, and that its presence resulted from illicit use.

Amphetamine was detected (>0.05 mg/L) in only 44 of the 146 cases, and in no cases over the same period was it ever detected in the absence of methamphetamine. The median amphetamine concentration was 0.17 mg/L, although in six cases it exceeded 0.5 mg/L, and in two of these it exceeded 1 mg/L (1.10 mg/L, and 2.20 mg/L). In these latter two cases, the ratio of amphetamine to methamphetamine concentrations were 0.67 and 0.38. In all cases where amphetamine was detected, the median amphetamine/methamphetamine ratio was 0.22. In five cases the amphetamine concentration exceeded that of methamphetamine, but in each case the sum of both drugs was less than 1.0 mg/L. Amphetamine is a primary metabolite of methamphetamine but is also a drug of abuse in its own right, and its origin in these cases could therefore not be determined with certainty, although the low concentrations and the presence of methamphetamine would tend to suggest metabolism. Pharmacokinetic studies (19,20) have shown that than amphetamine concentrations in the blood are typically less than 5% that of the methamphetamine concentration, and do not approach this level until 5–10 hours after administration depending on the route. It is likely therefore that elevated amphetamine concentrations or amphetamine/methamphetamine ratios reflect extensive use over time. The data discussed below, however, and the conclusions based thereon, deal with quantitative methamphetamine concentrations found, and should be used with caution in the interpretation of cases with elevated amphetamine concentrations (>1.0 mg/L), or in cases where amphetamine is present in great excess of methamphetamine.

Cases were designated as shown in Table 1, together with the median and range of methamphetamine concentrations. The average age of fatalities reviewed was 34 years (range 18–63 years), and 85% were male. This is essentially identical to the abusing population identified in the DAWN data set (15).

Of the 146 cases reviewed, 92 were determined to be drug related, while 52 were drug caused (see Table 1). There were two deaths in which the limited information available (cause and manner of death) did not unequivocally clarify the relationship of the natural disease process to drug use and the actual role of methamphetamine in the death. There was substantial overlap in methamphetamine concentration between drug related deaths (0.05–9.30 mg/L) and drug caused deaths (0.05–68.90 mg/L), although the highest concentrations were seen in the unintentional (accidental or undetermined) drug caused deaths. These deaths will be further discussed based on classification by manner of death and causal relationship of the drug to death.

Drug-Related Deaths—Accidents (Traffic)

Of the 33 accidental drug-related deaths, 20 were traffic accidents. Four (20%) were female, 16 (80%) male, median age 30. In 3 cases the subject was a pedestrian, while in 17 the subject was known to be the driver, and in all but one case was determined from the investigation to be the causing driver (see Table 2). The methamphetamine levels in the drivers ranged from 0.05 mg/L to 2.6 mg/L. Alcohol was present in only four of the 17 cases. Cannabinoids were present in three drivers, chlorpheniramine in one, cocaine or its metabolites in two, and morphine in two. The driving behavior which resulted in the accident was determined from the investigator's report. By our definition, traffic deaths are generally traumatic, and therefore not directly drug caused; however, in the majority of the cases, the effects of the drug use most likely contributed to the collision.

A previous study of driver behavior, demographics, statements, and signs and symptoms of intoxication in 28 persons arrested for methamphetamine-related traffic violations (16) explored the

TABLE 1—*Drug caused/drug related determinations in methamphetamine positive deaths (*n = *146).*

Role of Methamphetamine	# of Cases	Methamphetamine Concentration Range (median) (mg/L)
Indeterminate (2)	2	0.32– 0.41 (n/a)
Drug Related (92)		
accident—traffic	20	0.05– 2.60 (0.35)
accident—other	13	0.10– 6.50 (0.42)
suicide	18	0.05– 1.64 (0.47)
homicide	39	0.03– 9.30 (0.55)
undetermined	2	0.10– 3.40 (n/a)
Drug Caused (52)		
accident—traffic	0	n/a
accident—other	30	0.05–68.90 (0.38)
suicide	3	0.20–36.70 (0.65)
homicide	1	0.46 (n/a)
undetermined	18	0.10–24.20 (0.48)

TABLE 2—*Driving behavior in fatally injured drivers. All drivers were determined from the investigation to be the causing party except in the one case noted.**

Age	Sex	Meth. (mg/L)	Amp. (mg/L)	Alcohol (g/100 mL)	Driving Behavior
32	m	0.05	—	neg	Drifts out of lane of travel on curve†
32	m	0.10	—	neg	High speed, drifts out of lane of travel on a curve
33	f	0.18	0.40	0.32	Drifts out of lane of travel on curve‡
27	f	0.20	0.20	0.14	High speed, drifts out of lane of travel on curve
22	m	0.21	—	neg	Struck by other vehicle crossing center line§
37	m	0.28	—	neg	High speed pursuit, leaves road on curve
40	m	0.30	—	neg	Drifted off road onto shoulder
25	m	0.40	0.05	neg	Crash during high speed police pursuit of stolen vehicle
23	m	0.80	0.30	neg	Crosses into oncoming traffic
40	m	1.00	—	0.17	High speed, left road on curve
32	m	1.08	—	neg	Tractor trailer drifts off roadway
42	m	1.35	0.14	neg	Tractor trailer drifts off roadway
45	m	1.57	0.22	neg	Crosses into oncoming traffic‡
37	m	1.90	—	neg	Crosses into oncoming traffic†
45	m	1.90	—	neg	Crosses centerline striking other vehicle
24	f	2.20	0.23	0.09	High speed erratic driving, crosses center-line
23	m	2.60	0.20	neg	Leaves lane of travel hitting barrier

*Cocaine.
†Cannabinoids.
‡Opiates.
§Non-causing driver.

likely contribution of methamphetamine use to traffic accidents, including increased risk taking, and driving while impaired through drug withdrawal or abstinence syndrome, following an episode of methamphetamine use. There are some marked similarities between the populations in the current study and that earlier report. The demographics of both populations are identical in terms of age, gender, and toxicology findings. Secondly, the most prominent factors of accident causation in both populations were drifting out of lane of travel and high speed/reckless driving. Finally, the range of blood methamphetamine concentrations in both populations was also identical—0.05 to 2.6 mg/L. These similarities support the conclusions of that earlier study regarding the dangers associated with driving while impaired either by the methamphetamine itself, or by the fatigue and related symptomatology experienced during methamphetamine withdrawal.

Drug-Related Deaths—Accidents (nontraffic)

These 13 deaths were a result of falls (3 cases), gunshot wounds (3 cases; 1 head, 1 chest, 1 torso), drowning (2 cases), asphyxiation (2 cases), carbon monoxide poisoning, traumatic asphyxia, and electrocution (1 case each). Using available information, it is not possible to state with any confidence the specific role that the drug played in these deaths, nor whether death would have been avoided had the drug not been used. The concentrations encountered (0.10 to 6.50 mg/L) cover a broad range and include three above 1 mg/L, a level considered toxic or potentially lethal by most objective toxicologic studies/reports or tabulated guides to interpretation (see Table 3).

Drug-Related Deaths—Suicides

The majority of the suicides (18 of 21 total) were drug related rather than caused by acute overdose. The causes of death were gunshot wound (11 cases; 9 head, 2 chest), CO poisoning (3 cases), hanging (2 cases) and falls (2 cases). This pattern is consistent with suicide modalities in the general population of King county, Washington's most populous county, and is not remarkable. In most cases it was not possible to determine precisely the factors which led to the decision to commit suicide. However methamphetamine use could promote suicidal behavior, because 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.

TABLE 3—*Literature guides to interpretation of blood methamphetamine concentrations.*

Author	Ref	Therapeutic (mg/L)	Toxic (mg/L)	Fatal (mg/L)
Garriott	(21)	0.04	—	1.0
Baselt	(22)	0.03	0.15–0.51	0.8–40
Winek	(23)	0.01–0.05	0.6 –5.00	>10
Clarke	(24)	0.01–0.05		0.1, 0.6
Stead and Moffat	(25)	0.03		>0.10 (mean 0.23)
Nagata et al.	(26)	<0.30*	0.30–3.00	>4.5
Uges	(27)	0.01–0.05	0.20–1.00	—

*Lower limit of toxic effects of abuse.

Drug-Related Deaths—Homicides

Thirty-nine of forty homicides were methamphetamine-related, with the cause of death being either gunshot wound (31 cases; 21 head, 8 chest, 1 head/chest, 1 torso), 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. By way of comparison, Logan et al. (28) have reported survival of a subject with a blood methamphetamine concentration of 9.50 mg/L, demonstrating that even markedly elevated methamphetamine concentrations are not always lethal. Furthermore, in this series, the cause of death in those cases with higher methamphetamine concentrations was invariably gunshot wound. The possibility of contamination of blood samples in trauma cases cannot be excluded, however, in all cases attempts were made to collect blood from intact vessels. The presence of these high levels in ambulatory individuals illustrates one of the difficulties with designating a presumptive lethal level for the drug, or determining cause of death solely from toxicology

results. Although these extremely high levels did occur in some cases, most of the homicide victims had concentrations of methamphetamine which were generally much lower (the median was 0.5 mg/L, 83% had levels less than 1.0 mg/L), and are probably most representative of the range of concentrations routinely achieved in live methamphetamine abusers.

Drug Caused Deaths

This is the most significant classification with respect to evaluating the toxicity of methamphetamine, since it includes, by definition, death resulting from the toxic effects of the drug. There were a total of 52 deaths in this category. These drug caused deaths were further subdivided into three groups for discussion and consideration of the blood drug concentrations: overdoses of methamphetamine alone (in which drugs with little acute toxicity such as caffeine, nicotine and cannabinoids; also amphetamine may have been present as a metabolite); overdoses of methamphetamine in combination with other drugs; and drug overdoses with co-existent significant underlying natural disease, as indicated on the death certificate. The ranges and median concentration data are shown in Table 4.

Methamphetamine/Drug Combination Caused Deaths (n = 25)

Of the 25 drug caused deaths where methamphetamine was present in combination with other drugs, the major combinations were as follows: methamphetamine and morphine—9; methamphetamine and cocaine—6; methamphetamine, cocaine and morphine—3; methamphetamine, diazepam and methadone—2; propoxyphene, chlorpheniramine, amitriptyline, and diphenhydramine were present in one case each. Alcohol was present in only four of the 25 cases. The median lethal concentration of methamphetamine when other drugs were present was 0.37 mg/L. Obviously in these cases, the actual concentrations of the other drugs present will often be significant and must be considered also.

Methamphetamine-only Drug Caused Deaths (n = 13)

In 13 of the cases reviewed, methamphetamine was the only drug present in significant quantities, and there was no significant natural disease noted. In several of these cases cannabinoids were present; however, their toxicity is not believed to be significant in terms of causing death. Alcohol testing was negative in all these cases. The median methamphetamine concentration in this group was 0.96 mg/L, and the range was 0.09–18.0 mg/L.

Methamphetamine/Disease Caused Deaths

There were 14 methamphetamine caused deaths where there was underlying natural disease present that was significant enough to be designated as a cause or contributory cause on the death certificate.

TABLE 4—*Classification of drug caused deaths (*n = *52) according to role played by methamphetamine.*

Classification	# cases	Methamphetamine Concentration Range (Median) (mg/L)
Methamphetamine-only	13	0.09–18.00 (0.96)
Methamphetamine and other drugs	25	0.05–68.90 (0.37)
Methamphetamine and disease	14	0.09– 0.47 (0.36)

The natural disease processes included atherosclerotic cardiovascular disease (8 cases); subarachnoid hemorrhage/ruptured berry aneurysm (2 cases); asthma (1 case); chronic obstructive pulmonary disease (1 case); and other heart disease (hypertrophic cardiomyopathy, endocarditis, one each). In the original death certificates, 11 of these deaths were originally classified as natural deaths. After review of toxicology reports and available autopsy and investigative information, 14 cases were identified in which methamphetamine concentrations were greater than the upper limit of the therapeutic range (0.05 mg/L, see Table 3), with a range of 0.09–0.47 mg/L, and a median concentration of 0.39 mg/L. Median concentrations are more meaningful than mean concentrations in a non-normally distributed populations such as this, since means tend to be biased high as a result of massive overdoses.

There were two cases originally certified as natural deaths (malignant melanoma with brain metastases, and end stage liver disease with multiple organ failure and lactic acidosis), in which the methamphetamine levels were relatively high (0.41 and 0.32 mg/L, respectively), and could be considered to be in the potentially lethal range. However, there was insufficient information about the circumstances of death and the clinical and pathologic aspects of the natural disease process to allow determination of significance of the methamphetamine concentrations relative to cause of death.

Other tissues were not analyzed quantitatively in any of the patients discussed above, however, methamphetamine tissue distribution has been reported elsewhere (28).

A nomogram was constructed showing the cumulative proportion of fatalities occurring with respect to blood methamphetamine concentration for each group of drug caused deaths (Fig. 1). Comparative information for drug related deaths is also included. This approach to the data presentation is modeled after earlier examples by Stead and Moffat (29). The figure (and summary median and percentile data in Table 5) illustrate that within the population studied, significantly higher concentrations of methamphetamine were required to cause death in the absence of other confounding factors such as poly-drug use, or disease.

The data for the drug related deaths can be viewed as a control group, being those people with significant amounts of methamphetamine present which clearly did not cause death. This comparison reveals that drug concentrations were higher in the group of methamphetamine-only drug caused death (median 0.96 mg/L) than in the control group (median 0.42 mg/L), reflecting the increased risk of toxicity at higher blood concentrations. Nonetheless, 25% of the fatalities resulting from methamphetamine use alone still occurred with blood concentrations below 0.30 mg/L, with one as low as 0.09 mg/L. Methamphetamine concentrations were lowest in the deaths caused by methamphetamine in combination with either other drugs (median 0.37 mg/L), or natural disease (median 0.36 mg/L), and were not significantly different from one another. There was in fact, substantial overlap between drug caused and drug related deaths, particularly if the extremely high levels are excluded. This is in agreement with a previous study of methamphetamine related deaths in San Diego County, in which Bailey and Shaw (30) showed that there was no significant difference between mean tissue concentrations of methamphetamine in accidental overdoses (similar to our drug-caused deaths) and in homicides (similar to our drug-related deaths), with blood concentrations ranging from 0.02 to 3.05 mg/L.

Comment

There was a marked incidence of homicidal or suicidal violence associated with the use of methamphetamine in this population.

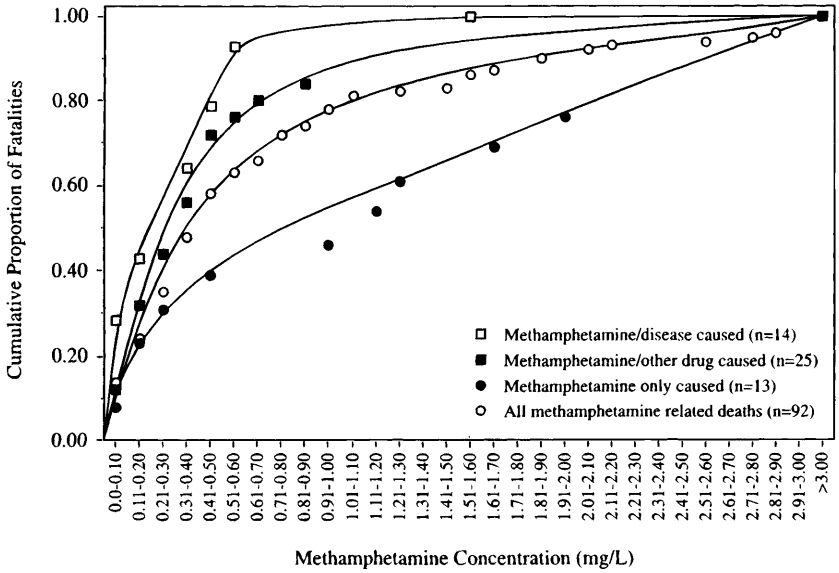

FIG. 1—*Nomogram for comparison of cumulative rates of fatalities with corresponding blood methamphetamine concentrations. Data is shown for deaths where methamphetamine was found the presence of natural disease, deaths where methamphetamine was found in the presence of other drugs, deaths where methamphetamine was present but did not directly cause the death (methamphetamine related), and deaths where methamphetamine was determined to be the sole causative factor.*

Over the same period of time, in those deaths in Washington state in which the victim tested positive for morphine, only 4% of these were homicide victims and 6% were suicides. By comparison, in those decedents testing positive for cocaine use, another stimulant, 18% were homicide victims and 9% were suicides. This compares to 27% homicides and 15% suicides in cases testing positive for methamphetamine. Much anecdotal evidence has suggested an association between violence and stimulant use in general, and methamphetamine use in particular. Logan (16) reported that violent behavior in subjects arrested for DUI, who later tested positive for methamphetamine, was more consistently noted in individuals with blood concentrations greater than 1 mg/L. Baselt (22) has noted a toxic range beginning at concentrations of 0.15 mg/L, often associated with violent and irrational behavior. In a study of patients suffering from amphetamine psychosis, loss of concentration, paranoia, delusions, and hallucinatory behavior were common (8). These patients had amphetamine concentrations in the range 0.08 to 0.64 mg/L; however, there was no correlation between the actual blood amphetamine concentration and the extent of the symptoms.

There are differing reports on the incidence of psychosis associated with abuse of amphetamines. In a study where methamphetamine was administered intravenously *ad lib* to methamphetamine abusers, Bell (5) documented psychosis in all subjects who persisted with the study, after from 1 to 90 hours of continuous use. Ellinwood (9) reported frequent psychotic reactions in patients he evaluated, while Hall and coworkers (10) felt that its incidence, based on evaluation of hospital patients was less common than reported by Ellinwood.

TABLE 5—*Blood methamphetamine concentrations (mg/L) associated with proportion of fatalities in each group.*

	Proportion of Fatalities			
	25%	50%	75%	90%
Methamphetamine-only overdoses	0.30	0.96	1.92	2.70
Methamphetamine and other drugs	0.17	0.33	0.60	1.55
Methamphetamine and disease	0.10	0.21	0.43	0.75
All drug related	0.22	0.42	0.92	2.20

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. (31) have 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 (32). Drug use was also reported as being common in both victims and perpetrators of domestic violence (14). 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 (33); the development in co-users of paranoia, violent tendencies, impaired judgment, and poor impulse control. These factors can all engender an atmosphere in which false beliefs, minor disagreements, or misunderstandings can quickly escalate to assault and homicide. Although there is much anecdotal evidence, there are no objective data clearly demonstrating the causal link between violent behavior and methamphetamine use/blood concentration. In our series, none of the perpetrators of the homicides included had been tested for drug use proximate to the offense. That type of testing would more specifically delineate the role of methamphetamine use in violent crime.

This study confirmed previous work, demonstrating the contribution of methamphetamine use to traffic accidents and resultant fatalities. Circumstantial information and blood methamphetamine concentrations were remarkably similar to earlier findings, with the clearly nonlethal concentrations causing identifiable and reportable symptoms resulting in impaired driving.

The interpretation of methamphetamine concentrations must be done in the context of an individual death, considering investigative and pathologic findings. In this study, there was considerable overlap of methamphetamine concentrations between drug caused and drug related deaths. Although the highest concentrations were

found in the drug caused unintentional deaths, very high concentrations were also identified in deaths clearly not causally related to methamphetamine. Median methamphetamine concentrations were similar in drug caused deaths associated with significant natural disease and deaths caused by methamphetamine in combination with other drugs. Fifty percent (median) of methamphetamine-only deaths occurred at concentrations below 1.0 mg/L, while 75% mortality occurred at levels less than 2.0 mg/L. This is in contrast to 75% mortality in combined drug caused deaths when methamphetamine concentrations exceeded 0.50 mg/L. Our data are generally in agreement with literature compilations, and indicate that most methamphetamine deaths occur with blood concentrations greater than 0.5 mg/L, but can occur with levels as low as 0.05 mg/L, usually in conjunction with other drugs present or concomitant natural disease.

The interpretation of methamphetamine concentrations in deaths in which there is sufficient natural disease to account for death is a difficult issue. Methamphetamine is known to cause hypertension, tachycardia, atrioventricular arrhythmia, and myocardial ischemia. However, the incidence of patients who present with cardiovascular effects from methamphetamine appears to be lower than that seen with cocaine. Methamphetamine does not cause vasospasm, and has not been reported to cause platelet aggregation, both of which are seen with cocaine (35–37). Morphologic alterations similar to those seen in catechol-mediated cardiotoxicity have been seen in animal models of amphetamine poisoning (38). Islam et al. (39) demonstrated light microscopic changes in the myocardium of rats treated with daily intraperitoneal injections of methamphetamine; changes included myocyte atrophy, hypertrophy, eosinophilic degeneration and disarray, edema, myolysis, fibrosis, and vacuolization. Clinically, reversible cardiomyopathy has been described (36,40,41), but sudden death appears to be most frequently related to arrhythmia. Other authors have associated acute aortic dissections and rupture of congenital berry aneurysms with the hypertensive and tachycardic effects of methamphetamine (42), and have postulated that chronic use of methamphetamine may have an etiologic role in the formation of berry aneurysms (43). Hemorrhagic and ischemic stroke is also well described, as are cases of necrotizing vasculitis, which may be associated with intracerebral hemorrhage (36). Thus, the histologic and physiologic effects of methamphetamine administration are similar to those seen with catecholamine administration and/or toxicity.

The pharmacologic effects of methamphetamine might be expected to exacerbate any pre-existing cardiovascular disease, such as coronary atherosclerosis or cardiomyopathy. As noted earlier, we found significant overlap of methamphetamine blood concentrations between deaths that are clearly caused by methamphetamine overdose, and deaths clearly caused by violence, where the blood methamphetamine concentration is not causally related to death. Thus, in cases where there is cardiovascular natural disease sufficient to account for death, but not an unequivocal natural cause of death (such as a rupture of an acute myocardial infarct or a massive pulmonary thromboembolism), and where the blood methamphetamine concentration is higher than the therapeutic range ($>$0.05 mg/L), it seems reasonable to consider the death to be unnatural, related to the combined effects of both the natural disease and the methamphetamine intoxication, as cause and contributory cause, depending on circumstances of death. A similar argument might be applied in cases of ruptured berry aneurysm, spontaneous intracerebral hemorrhages, dissecting aortic aneurysm, and any death in which the pharmacologic effects of methamphetamine might be considered to exacerbate underlying natural disease. In our study, when this scheme was used in the classification of natural deaths, with blood concentrations greater than 0.05 mg/L considered to be potentially toxic, nine of eleven cases originally classified as natural were reclassified as drug caused.

In addition, because methamphetamine concentrations should not be interpreted in isolation, it is important that complete autopsies be performed, in order to understand and properly certify deaths. A high concentration of methamphetamine cannot in isolation be interpreted as evidence that death was caused by acute overdose. Similarly, in any death thought to be caused by natural disease, in which illicit (nonprescription) methamphetamine is present in low concentration, consideration should be given to designating methamphetamine intoxication as a contributory cause of death. Certain known clinical scenarios may more clearly exclude or confirm methamphetamine as a cause of death, although in decedents with unattended deaths, no such information may be available.

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