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Postmortem diagnosis and toxicological validation of illicit substance use

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Abstract

The present study examines the diagnostic challenges of identifying ante-mortem illicit substance use in human postmortem cases. Substance use, assessed by clinical case history reviews, structured next-of-kin interviews, by general toxicology of blood, urine, and/or brain, and by scalp hair testing, identified 33 cocaine, 29 cannabis, 10 phencyclidine and 9 opioid cases. Case history identified 42% cocaine, 76% cannabis, 10% phencyclidine, and 33% opioid cases. Next-of-kin interviews identified almost twice as many cocaine and cannabis cases as Medical Examiner (ME) case histories, and were crucial in establishing a detailed lifetime substance use history. Toxicology identified 91% cocaine, 68% cannabis, 80% phencyclidine, and 100% opioid cases, with hair testing increasing detection for all drug classes. A cocaine or cannabis use history was corroborated by general toxicology with 50% and 32% sensitivity, respectively, and with 82% and 64% sensitivity by hair testing. Hair testing corroborated a positive general toxicology for cocaine and cannabis with 91% and 100% sensitivity, respectively. Case history corroborated hair toxicology with 38% sensitivity for cocaine and 79% sensitivity for cannabis, suggesting that both case history and general toxicology underestimated cocaine use. Identifying ante-mortem substance use in human postmortem cases are key considerations in case diagnosis and for characterization of disorder-specific changes in neurobiology. The sensitivity and specificity of substance use assessments increased when ME case history was supplemented with structured next-of-kin interviews to establish a detailed lifetime substance use history, while comprehensive toxicology, and hair testing in particular, increased detection of recent illicit substance use.

Keywords

addiction; biological matrix; brain; drug abuse; hair toxicology; Postmortem Substance Abuse Assessment Questionnaire; substance use disorders

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Introduction

Substance use changes brain function both acutely and chronically. Human postmortem brain provides the only direct means to examine the cellular neurobiology associated with human substance use disorders, but such studies are associated with a particular set of diagnostic challenges. As retrospective characterization of the nature and extent of the ante-mortem illicit substance use is a prerequisite for identifying disorder-specific changes in neurobiology for any disease or disorder employing human postmortem cases, an examination of the methods for establishing substance use and substance use history is warranted.

Several diagnostic instruments have been specifically validated to assess substance use, abuse and dependence in living subjects (McLellan *et al*., 1992; American Psychiatric Association, 1994; Chatterji *et al*., 1997; Pierucci-Lagha *et al*., 2005; Hasin *et al*., 2006), but none address retrospective assessments of ante-mortem substance use in postmortem cases. Instead, current practice in studies of neuropsychiatric disorders is to establish a case history using all available sources of information, including ME reports, next-of-kin informants, and medical and/or legal records (Hill *et al*., 1996; Roberts *et al*., 1998; Deep-Soboslay *et al*., 2005; Lewis, 2002). Significantly different individual case histories may, however, be depicted by different sources, as demonstrated for schizophrenia and mood disorders (Deep-Soboslay *et al*., 2005). Such variability likely also exists for information regarding illicit substance use, and may be attributable to unreliable ante-mortem self-reports of substance use (Myrick *et al*., 2002; Tassiopoulos *et al*., 2003; Musshoff *et al*., 2006), either by misrepresenting use details or by unknowingly using adulterated drugs. Furthermore, next-of-kin informants may lack the knowledge, ability and/or willingness to disclose illicit substance use and associated consequences.

Toxicological examination is of particular importance in the characterization of substance use disorders, as it establishes recent use and may even reveal additional aspects of recent substance use not identified by other case history. Specifically, interpretation of toxicological data must take into account that different biological samples, such as urine, blood, brain and hair, provide unique pharmacokinetic information, with differing biomarkers and concentrations yielding variable detection times (Huestis, Henningfield & Cone, 1992; Huestis, Mitchell & Cone, 1996; Henderson *et al*., 1996; Preston *et al*., 2002; Verstraete, 2004). For example, cocaine and its metabolites are easily detected in blood and urine, but with a narrow two to three day window of detection (Musshoff et al, 2006; Verstraete, 2004), whereas hair testing generally permits a retrospective view of several months (Nakahara, Takahashi & Kikura 1995; Henderson *et al*., 1996; Verstraete, 2004). Cannabinoids are rapidly cleared from blood, but may be quantified in brain when no longer detected in blood (Mura *et al*., 2005), and in hair from heavy chronic users for months after last drug exposure (Uhl and Sachs, 2004). Toxicology thus represents another complex, but important component of assessing ante-mortem substance use history.

We undertook a study of a set of substance use cases, which had been extensively researched with respect to case history and toxicology, to compare different sources of substance use history and toxicology, and examine correlations, advantages and limitations of each. Our findings highlights that information from multiple sources is crucial in assessing lifetime and recent substance use, and furthermore that comprehensive case history and toxicological examination are needed to cross-validate lifetime and recent ante-mortem drug use in any human postmortem cases employed for neurobiological research.

Materials & Methods

Source and selection of cases

Cases were donated by the next-of-kin to the Clinical Brain Disorders Branch (CBDB), NIMH through the Offices of the Chief Medical Examiner of the District of Columbia and of Northern Virginia. Informed consent was obtained in accordance with NIH Institutional and NIMH IRP policy (Protocol no. 90-M-0142).

Forty-two substance use cases, drug abuse (DA) cases DA1–42, with either a substance use history or toxicological evidence of substance use were identified in the CBDB brain repository, and further characterized by gene expression microarray analysis (Lehrmann *et al*., 2006), and by gas chromatography/mass spectrometry (GC/MS) analysis of cerebellar tissue (Lowe *et al*., 2006). Eight additional cases with other psychiatric diagnoses, DA43–50, were included for examination by the NIDA PSAAQ (below).

Case history review

The Autopsy Questionnaire (AQ), a brief next-of-kin telephone interview obtained at the time of donation, included a history of medical problems, psychiatric care or substance abuse treatment, and a general educational and social history. Available ME case information, including the autopsy report, death certificate, clinical history, pertinent medical history or circumstances that may have contributed to death, were reviewed. Follow-up family contact was attempted to obtain written release authorizations for medical records and to complete additional next-of-kin interviews, consisting of the Structured Clinical Interview for DSM-IV, Clinician Version (SCID-CV) (First *et al*., 1997, Miller *et al*., 2002), and the NIMH psychological autopsy (PA), adapted in part from Columbia University and University of Pittsburgh's PA questionnaires (Kelly and Mann, 1996; Deep-Soboslay *et al*., 2005). The NIDA PSAAQ, a semi-structured informant-based interview gathering retrospective information on lifetime substance use for deceased individuals (Supplementary Table 1), was piloted on 12 cases. The information obtained included substance(s) used, estimates on frequency and characteristics of use, hospitalizations, legal charges or court-mandated treatments, drug detoxification, medical interventions, or other details indicating drug use.

Toxicological evaluation

Toxicological results were obtained from the ME with supplementary toxicological testing to validate and extend the scope of drugs tested (National Medical Services, Willow Grove, PA). Left superior lateral cerebellum specimens from DA1–42 were examined by GC/MS for the presence of cocaine, amphetamines, phencyclidine, and opioids and metabolites (Lowe *et al*., 2006). Detailed toxicological data from this examination were previously published using the same case identifiers (Lehrmann *et al*., 2006). All ME and supplementary toxicologies of tissues and/or fluids are summarized under the general toxicology heading and the name of the parent drug (Table 1). Scalp hair testing, employing 1–4 cm scalp end hair, was undertaken for cocaine, cannabis, phencyclidine, opioids and amphetamines (Psychemedics Corporation, Culver City, CA) for 37 cases (Table 1).

Sensitivity and specificity (Tables 3–4)

Test sensitivity and specificity, which evaluate how well a screening test corroborates a reference method, was used to assess the ability of case history and toxicology from different sources to predict presence and absence of ante-mortem substance use in human postmortem cases. Sensitivity, evaluating the ability of a screening test to correctly identify substance use cases, was calculated as the proportion of cases reported positive by both screening test and reference ("true" positive cases) to all positive reference cases. Specificity, evaluating the

ability of a screening test to correctly identify the absence of substance use, was calculated as the proportion of cases reported negative by both screening test and reference ("true" negative cases) to all negative reference cases. False negative and false positive percentages corresponded to 100% less the sensitivity and specificity percentages, respectively.

Results

Establishing a case history from ME information and next-of-kin interviews (Table 2)

The PSAAQ was piloted on four substance use cases and eight cases with other psychiatric diagnoses. Substance use was identified by case history for 11 cases, of which ten by the PSAAQ, eight by the AQ and seven by ME documents. The PSAAQ corroborated a substance use history for 6/7 ME cases (86%) and no reported substance use history for 4/5 ME cases (80%), and further corroborated a substance use history for 7/7 AQ cases (100%) and no reported substance use history for 2/3 AQ cases (67%).

A more comprehensive picture of lifetime substance use was provided by the PSAAQ than by the AQ and ME documents. Overall, the PSAAQ provided information on a similar or larger number of drugs than the combined ME+AQ case histories for 9/11 cases (82%) with a substance use history, and for 10/11 cases (91%) with ME case histories and 8/8 cases (100%) with AQ interviews. The AQ identified more individual substances than ME case histories for 5/10 cases, and less than the ME in 3/10 cases, and agreed on no substance use in two cases. Additional information on the duration, frequency and/or type of use was obtained for eight PSAAQ cases, four AQ cases and two ME cases, while substance-use related treatment history and/or legal problems were recorded by the PSAAQ for seven cases, in three ME case histories and two AQ case histories.

Identification of substance use by source (Table 3)

Overall, case history and/or toxicology identified 33 cocaine, 29 cannabis, 10 phencyclidine, and nine opioid use cases. Toxicology (ME/supplementary toxicology and hair testing) identified more cases than case history (ME/next-of-kin) for cocaine (30 vs. 14), phencyclidine (eight vs. two) and opioid (nine vs. three) use cases. Case history and toxicology respectively identified 22 and 20 cannabis use cases. Next-of-kin interviews identified more cases than ME case histories for cocaine (ten and six cases, respectively), cannabis (16 and six cases), and opioids (four and three cases). ME case histories identified two phencyclidine cases, and next-of-kin one. ME toxicology, general toxicology and hair testing each identified cocaine and metabolites in 11, 15 and 24 cases, cannabinoids in four, 12, and 18 cases, phencyclidine in three, four and five cases, and opioids in four, six, and six cases. Supplementary toxicology of blood and/or brain added four cocaine, eight cannabis, two phencyclidine and two opioid use cases to those already identified by ME toxicology, corresponding to increases of 36%, 200%, 50% and 50%, respectively. Hair testing therefore identified the largest proportion of substance use cases.

Substance use identified by case history (Table 4)

Forty-three cases with a substance use history were examined to determine if presence or absence of a specific substance use history would be corroborated by general toxicology and/or by hair testing. Hair testing was more sensitive than general toxicology in validating a case history of cocaine (82% vs. 50%, respectively) and/or cannabis use (64% vs. 32%), while the limited number of phencyclidine and opioid cases prevented meaningful interpretation for these.

Toxicology corroborated a positive case history with moderate sensitivity for cannabis (64%) and cocaine (71%). A negative case history was corroborated by toxicology with high

specificity for cannabis (75%), phencyclidine (83%) and opioids (91%), and with a much lower specificity for cocaine (49%).

Substance use identified by toxicology and by hair testing (Table 5)

Substance use cases identified by toxicology and by hair testing were poorly corroborated by the case history for cocaine (40% and 38% sensitivity, respectively), phencyclidine (0% and 0%), and opioids (29 and 20%), and moderately-highly corroborated for cannabis cases (64% and 79%). In contrast, case history corroborated a negative toxicology and/or a negative hair test with moderate-high specificity for all substances (72–100%). Negative hair testing was similarly corroborated by general toxicology with high specificity (92–100%) for all substances, while general toxicology corroborated substance use identified by hair testing to variable degrees for phencyclidine (20% sensitivity), cocaine (42%), cannabis (53%) and opioids (60%).

Discussion

Neurobiological studies employing human postmortem brain depend on correct identification and characterization of both substance use and control cases. Presently, we found that different sources of case history and toxicology supply both confirmatory and complementary information needed for a comprehensive assessment of lifetime and recent ante-mortem substance use in human postmortem cases.

Case history

The PSAAQ interviews illustrated two important aspects of retrospective examination of ante-mortem substance use history. First, information on substance use from the AQ and ME rarely provided much detail as to the nature, pattern, frequency and manner of use, or of medical and legal consequences. This information was primarily accessed in structured follow-up interviews using the PSAAQ and SCID. Secondly, it was confirmed that while the next-of-kin may initially lack the knowledge, ability and/or willingness to disclose illicit substance use, such that they at first denied or minimized drug use, additional data on substance use was uncovered in follow-up interviews when direct questions pertaining to jail time, prescriptions and use of abuse-related treatment programs *etc.* were asked. The PSAAQ and DSM-IV-based next-of-kin interviews therefore helped facilitate and uncover information on substance use that informants may not initially have perceived as problematic, and in turn provided information that would help in assessing the nature of substance use, abuse or dependence.

A limitation of this study was that the next-of-kin were generally more guarded and less amenable to family contact and comprehensive interviews as compared to next-of-kin of donors with other psychiatric disorders. A major factor in why the current next-of-kin were less inclined to participate in follow-up interviews could be that homicide was the predominant manner of death for this cohort (71%). Furthermore, structured interviews could not be obtained for a number of cases due to changes in next-of-kin contact information. The AQ therefore proved an invaluable source of information in cases where follow-up interviews were not possible. As next-of-kin interviews significantly enriched information about lifetime substance use history, it would be important to increase the number of completed interviews. This may be accomplished in future studies if family informants are contacted within a shorter period from donation to interview; long enough to allow time to grieve but short enough that informants can be contacted. We previously found that contact within 2 years increased the likelihood of obtaining subsequent contact in our schizophrenia and mood disorders cohorts (Deep-Soboslay *et al*., 2005).

Toxicology

Evaluation of toxicological data require consideration of several factors, including the scope and limits of quantification of drugs examined, pharmacokinetics of drug disposition and excretion in different biological matrices, as well as the potential for false positive or negative results (Verstraete, 2004; Pragst and Balikova, 2006). In the course of re-evaluating general toxicology data using a comprehensive panel testing therapeutic and abused drugs in brain and blood, it became evident that a number of cases were incorrectly labeled as drug-negative. This was mainly due to the limited number of substances examined in the initial toxicological screenings. The expanded toxicological panel was further useful in detecting therapeutic drugs indicating other brain disease or neuropsychiatric conditions.

An attractive feature of toxicology is that it is more objective than self-reports of substance use (Mieczkowski, Newel & Wraight, 1998; Myrick *et al*., 2002; Tassiopoulos *et al*., 2004, 2006; Musshoff *et al*., 2006). In postmortem cases, reported history may also be confounded by a lack of ability, knowledge and/or willingness of the next-of-kin to disclose specific details of the deceased's illicit substance use. Case DA34 exemplifies these considerations, as next-of-kin denied any use in the AQ, yet acknowledged alcohol abuse in the PSAAQ, while both general toxicology and hair testing documented exposure to cocaine and metabolites and opioids (Table 2).

For smoked drugs-of-abuse such as crack-cocaine and cannabis, environmental contamination of hair may lead to inaccurate results, and debate continues as to whether specimen washing techniques and measurement of drug in wash solutions can differentiate environmental drug exposure. While absolute false positive rates cannot be extracted from our data, it is instructive to more closely examine data for cocaine hair testing. The low sensitivities ("true positives") for a cocaine-positive hair test being corroborated by either case history (38%) or by general toxicology (42%) indicates differences between sources in reporting cocaine use (Table 5). These differences do not necessarily reflect absolute false positive rates for hair testing, but more likely result from omissions in case history due to the ability, knowledge and/or willingness of the next-of-kin to disclose cocaine use, and to detection differences for cocaine between hair testing and the general toxicological matrices. This scenario was supported by the fact that there was no mention of a cocaine use history for 8/15 cases with recent cocaine intake, as indicated by a cocaine-positive general toxicology, while 10/11 cases with a recent cocaine intake had a cocaine-positive hair test (Table 1). Hair testing further appeared to reliably identify cocaine exposure in 9/11 cases with a documented cocaine use history (Table 4), with the two cocaine-negative hair tests representing cases with a history of heavy cocaine use many years in the past. Hair testing thus corroborated a cocaine use history with 82–100% sensitivity. Furthermore, a cocaine-negative hair testing was highly correlated (82%-92%) with a cocaine-negative case history and/or general toxicology (Tables 4 & 5). Moreover, that ante-mortem cocaine use might be underestimated if informed solely by case history and/or general toxicology of postmortem cases was suggested by considering that case history corroborated 79% cases with a cannabis-positive hair test, but only half that (38%) of cases a cocaine-positive hair test (Table 5). That it may be socially less acceptable to acknowledge cocaine than cannabis use was further indicated by the finding that all 11 cases with a cocaine-positive hair test, but no history or general toxicology findings of cocaine use, either had a cannabinoid-positive general toxicology (seven cases) or hair test (ten cases), and/or the sole illicit substance listed was cannabis (nine cases). Therefore, studies documenting that self-reporting, as well as urine toxicology, appeared to significantly underestimate cocaine use when compared to hair testing in living drug abusers (Mieczkowski *et al*., 1998;Musshoff *et al*., 2006), also extend to identification of cocaine use in human postmortem cases. While environmental contamination cannot be definitively excluded, the data above strongly point to hair testing as both a sensitive

and specific indicator of cocaine use, and as an important tool in evaluating cocaine use identified by case history and/or by general toxicology.

Detection of the cannabis metabolite 11-nor-9-carboxytetrahydrocannabinol in hair testing circumvented the problem of test specificity for cannabis, and increased the sensitivity of cannabinoid detection in cases with a cannabis use history from 32% by general toxicology to 64% by hair testing (Table 4). It has been suggested that the low incorporation of cannabinoids into hair may significantly underestimate the number of true positive cases (Nakahara *et al*., 1995). This was not evident in the present study, as hair testing corroborated cannabis use in 14/17 cases with a lifetime cannabis use history and in all cases with a recent cannabis use as evidenced by a cannabinoid-positive general toxicology (Table 1). That 53% of cases with a cannabinoid-positive hair test had a cannabinoid-positive general toxicology (Table 4) appears to be due to the different temporal perspectives afforded by the testing matrices, as 15/17 of cases with a cannabinoid-positive hair testing either had a cannabis-positive history and/or general toxicology. Cannabis use does, however, appear to be significantly underreported in that many ME laboratories do not include cannabis testing in routine death investigations. Presently, only one-third of cannabinoid-positive cases detected in subsequent testing of blood and/or brain were identified by ME toxicology (Table 3). These data suggest that currently active cannabis users can be reliably detected by hair testing, and that hair testing offers a suitable matrix for determining recent and regular ante-mortem use.

Most studies of human postmortem brain specimens, identified via a PubMed-based search spanning the last decade, relied on routine toxicological analysis of blood and/or urine. These toxicologies typically come from the ME, and are primarily meant to determine cause of death but not to assess all substance use. In studies of substance use that identified toxicological test matrices, analysis of blood was employed in all 32 studies, urine in 23, hair in 11, and brain in 10 studies. It would therefore seem that hair and brain toxicology are not uncommon in toxicological evaluations of human postmortem cases. These data, however, represent clusters of studies from a few research groups, with one of two groups responsible for 10/11 studies using hair testing also performing 6/10 studies using brain toxicology. Toxicological testing of human postmortem cases could therefore benefit from the added information provided by analysis of brain and hair.

Together, these findings underscore the importance of performing additional toxicological examinations of abused and therapeutic substances for all cases, including control cases where illicit or therapeutic substances are rarely suspected and therefore may not have been examined.

Implications

Our findings have relevance for studies into the neurobiology of other brain disorders, which require similarly well-characterized index and control groups to extract valid and clinically relevant data (Lewis 2002). It has been suggested that differences in diagnostic criteria may represent a major confounding factor in studies of postmortem neuropsychiatric cases (Hill *et al*., 1996; Roberts *et al*., 1998). Another potential confound is under-reporting of substance use or undiagnosed substance abuse or dependence. Estimates of the presence of substance use disorders concomitant with other neuropsychiatric disorders range from 10% to 75%, depending on the drug of abuse and clinical diagnosis (Grant *et al*., 2004; Conway *et al*., 2006; Swartz *et al*., 2006). The impact of comorbid substance use disorders with other neuropsychiatric disorders is illustrated by the significance of smoking history on gene expression in schizophrenia (Mexal *et al*., 2005), the presence of significant substance abuse in major depression (Sawamura *et al*., 2005), and of mood disturbances in abstinent methamphetamine abusers (London *et al*., 2004). Therefore, simultaneous assessment of substance use and other psychiatric disorders may assist efforts to identify disorder-specific changes.

Conclusions

Individual information sources provided an incomplete picture of ante-mortem substance use in human postmortem cases. That complex patterns of polysubstance use appear to be the norm, and not the exception, in substance users (Rounsaville, Petry & Carroll 2003), was also indicated in this study (Table 1). A lifetime substance use history, including patterns, manner and duration of use, should be addressed through clinical case history review and by next-of-kin interviews utilizing a combination of DSM-IV-based and substance use-specific structured interviews. Additionally, pairing the lifetime substance use history thus identified with comprehensive toxicological testing provided a better indication of exposure in the days and months prior to death, and - in a number of cases – also provided additional information on use of therapeutic and abused substances. Hair testing in particular enabled a significantly wider window of detection for most commonly abused substances than brain, blood or urine toxicology alone, and was further instrumental in establishing recent regular use. These protocols should be further developed and validated for use in human postmortem cases.

Thus, the adage “Absence of evidence is not evidence of absence” holds true for these studies, and therefore it is important to examine all sources of information, *i.e*. case history including pathology and toxicological information, for compounding evidence of the nature and type of substance use. Brain banks and studies employing human postmortem brain may therefore increase the validity of studies correlating neurobiological parameters with substance use or other neuropsychiatric brain disorders through combining structured interviews with comprehensive toxicological testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Case history and toxicological evaluation

Case history (Hx) was derived from Medical Examiner (ME) documents and from next-of-kin interviews. Manner and cause of death (MOD and COD, respectively) is indicated for each case. MOD: A – accidental, H – homicide, N – natural, S – suicide, and U – undetermined. COD: AI – acute intoxication, ALC – chronic and acute alcoholism, AMI – acute myocardial infarction, ASPX – asphyxiation, CA – cardiac arrythmia, GSW – gunshot wound, HCVD – hypertensive cardiovascular disease, IH – intestinal hemorrhage, MGSW – multiple GSWs, OP – opiate poisoning, PNEU - pneumonia, SP – salicylate poisoning, SW – stabwound, UGIH – upper gastrointestinal hemorrhage.

Drug abuse (DA) cases DA1–42 were characterized by a GC/MS analysis of cocaine, amphetamines, opioids and metabolites in cerebellum (CER) (Lowe *et al.*, 2006), and reported in a cDNA microarray study of these cases (Lehrmann *et al.*, 2006). General toxicology summarizes ME, supplementary and cerebellar toxicology for each case under the name of the parent drug of abuse. The matrix where positive toxicological results were obtained is indicated: blood (BL), brain (BR), CER (GS/MS study), urine (UR) or vitreous humor (VIT), is indicated. Negative toxicology results are indicated by a dash. Scalp hair testing examined the presence of cocaine, cannabis, phencyclidine, opioids, and amphetamines. *Abbreviations*: 6AM – 6-acetyl morphine, CER –cerebellum, COC – cocaine, COD - codeine, cTHC – 11-nor-9-carboxy-tetrahydrocannabinol, DEXM – dextromethorphan, EtOH – alcohol, M? –unspecified test matrix, MDMA – 3,4-methylenedioxymethamphetamine (Ecstasy), MOR – morphine, MTD – methadone, N/A – not available, NIC –nicotine, N/R – nothing reported, OXYC – oxycodone, PCP – phencyclidine, THC – delta-9-tetrahydrocannabinol.

SUBSTANCE USE: CASE HISTORY					GENERAL TOXICOLOGY									HAIR TESTING
CASE	**MOD**	**COD**	**MEDICAL EXAMINER**	**NEXT-OF-KIN**	**PCP**	**COC**	**THC**	**MOR**	**MTD**	**DEXM**	**COD**	**NIC**	**EtOH**	**COC, PCP, THC, OPIOIDS, cTHC**
DA1	H	GSW	N.R.	Cannabis	-	-	-	-	-	-	-	BR	-	cTHC
DA2	H	GSW	Crack-cocaine, cannabis	Crack-cocaine, cannabis, alcohol	-	-	-	-	-	-	-	BL	BL/VIT	COC, cTHC
DA3	H	GSW	N.R.	Crack-cocaine	-	CER	-	-	-	-	-	-	BL/VIT	COC, cTHC
DA4	N	HCVD	Crack-cocaine, alcohol	Nicotine	-	-	-	-	-	-	-	-	BL/VIT	COC
DA5	H	SW	N.R.	Crack-cocaine	-	BL/CER	-	-	-	-	-	-	BL	COC
DA6	N	AI	Cannabis, nicotine	Cocaine, heroin, cannabis, alcohol, nicotine	-	BL/UR/CER	-	-	-	-	-	-	BL/VIT	N/A
DA7	H	GSW	Crack-cocaine, alcohol	N/A	BL	-	-	-	-	-	-	-	BL	N/A
DA8	H	GSW	Cannabis distribution	N/A	-	-	BL	-	-	-	-	BL	-	COC, cTHC
DA9	N	AMI	N.R.	N/A	-	CER	-	-	-	-	-	-	BL	-
DA10	H	MGSW	N.R.	N/A	-	-	BL	-	-	-	-	BL	-	COC, PCP, cTHC
DA11	H	MGSW	Cannabis	N/A	-	-	M?	-	-	-	-	-	-	COC, cTHC
DA12	H	SW	Alcohol	N/A	-	-	-	-	-	-	-	-	BL/UR	N/A
DA13	H	SW	N.R.	N/A	-	BL/UR/CER	-	-	-	-	-	BL	BL/UR	COC
DA14	H	GSW	N.R.	Nicotine	-	-	BL	-	-	-	-	-	BL	N/A
DA15	N	UGIH	Alcohol	Cocaine, cannabis, alcohol, nicotine, Rx	-	-	-	-	-	-	-	BR	-	N/A
DA16	H	SW	N.R.	Alcohol, nicotine	-	BL/UR/CER	-	-	-	-	-	-	BL/VIT	N/A
DA17	H	GSW	N.R.	N/A	-	-	BL	-	-	-	-	-	BL	cTHC
DA18	H	GSW	N.R.	Cannabis, alcohol, nicotine	-	BL/CER	BL	-	-	-	-	-	BL/VIT	COC, cTHC

SUBSTANCE USE: CASE HISTORY					GENERAL TOXICOLOGY									HAIR TESTING
CASE	**MOD**	**COD**	**MEDICAL EXAMINER**	**NEXT-OF-KIN**	**PCP**	**COC**	**THC**	**MOR**	**MTD**	**DEXM**	**COD**	**NIC**	**EtOH**	**COC, PCP, THC, OPIOIDS, cTHC**
DA19	H	GSW	N.R.	Substance abuse Hx	-	-	BR/M?	-	-	-	-	BR	-	N/A
DA20	H	MGSW	N.R.	Cannabis	BR/BL	-	-	-	-	-	-	BR	BL	N/A
DA21	N	PNEU	PCP, cannabis, alcohol, nicotine	N/A	-	-	-	-	-	-	BR/CER	-	-	N/A
DA22	A	AI	Cocaine, heroin, methadone	Cocaine, cannabis, methadone, alcohol, Rx	-	BL/UR/CER	-	UR	BL/UR	-	UR	-	-	COC
DA23	H	GSW	N.R.	Cannabis	-	-	-	-	-	-	-	-	BL/UR	COC
DA24	H	GSW	N.R.	Cannabis	-	-	BL	-	-	-	-	BL	-	COC, cTHC
DA25	H	MGSW	N.R.	Cannabis, alcohol	-	-	BL	-	-	-	-	BL	-	COC, PCP, cTHC
DA26	H	SW	N.R.	N/A	-	BR/CER	-	-	-	-	-	-	-	N/A
DA27	H	SW	N.R.	N/A	UR	-	UR	-	-	-	-	-	-	COC, PCP, cTHC
DA28	H	GSW	N.R.	Crack-cocaine	-	BR/BL/CER	-	-	-	-	-	BR	-	COC, MOR, 6AM
DA29	H	GSW	N.R.	Cannabis, alcohol	-	-	BL	-	-	-	-	-	BL	COC, PCP, cTHC
DA30	H	GSW	N.R.	Cocaine, other	-	BL/CER	-	-	-	-	-	BL	BL/BI	COC, cTHC
DA31	H	GSW	N.R.	Cannabis	-	-	-	-	-	-	-	BR	-	COC, cTHC
DA32	H	MGSW	N.R.	N/A	-	BR/BL/CER	-	-	-	-	-	-	BL/M?	COC
DA33	A	AI	Crack-cocaine, alcohol, nicotine	N/A	-	BL/UR/CER	-	BL/UR/CER	-	-	UR	-	-	COC, MOR, 6AM, COD, OXYC
DA34	A	AI	Alcohol	Alcohol	-	BL/UR/CER	-	BL/UR/CER	-	-	-	-	-	COC, MOR, 6AM, COD
DA35	H	GSW	N.R.	Cannabis	UR	-	-	-	-	-	-	-	-	cTHC
DA36	N	HCVD	N.R.	Cocaine, alcohol, nicotine, polysubstance abuse	-	-	-	-	-	-	-	-	-	COC, MOR, 6AM
DA37	H	GSW	N.R.	Cannabis	-	-	BL	-	-	-	-	BL	-	COC, cTHC
DA38	S	GSW	Alcohol	Cannabis, alcohol	-	-	-	-	-	-	-	BR	-	cTHC
DA39	H	SW	N.R.	Alcohol, nicotine	-	BL/UR/CER	-	-	-	-	-	BL	-	N/A
DA40	N	ALC	Cannabis, alcohol	Alcohol	-	-	-	-	-	-	-	-	BL/VIT	-
DA41	N	AS	N.R.	Cocaine, alcohol	-	-	-	-	-	-	-	-	-	OPIOIDS
DA42	H	GSW	N.R.	Cannabis	-	-	-	-	-	-	-	-	-	COC, PCP, cTHC, MDMA
DA43	U	GSW	N.R.	Alcohol	-	-	-	-	-	-	-	-	-	N/A
DA44	A	SEPSIS	N.R.	N.R.	-	-	-	-	-	-	-	-	-	-
DA45	N	CA	Alcohol	Alcohol	-	-	-	-	-	-	-	-	-	N/A
DA46	A	OP	Morphine, Rx	Morphine, methadone, alcohol, Rx	-	-	-	BL	-	-	-	-	-	MOR, COD, OXYC

SUBSTANCE USE: CASE HISTORY					GENERAL TOXICOLOGY									HAIR TESTING
CASE	**MOD**	**COD**	**MEDICAL EXAMINER**	**NEXT-OF-KIN**	**PCP**	**COC**	**THC**	**MOR**	**MTD**	**DEXM**	**COD**	**NIC**	**EtOH**	**COC, PCP, THC, OPIOIDS, cTHC**
DA47	N	AMI	PCP, cannabis, alcohol, other	PCP, cocaine, cannabis, alcohol, other	-	-	-	-	-	-	-	BL	-	cTHC
DA48	N	IH	Alcohol	Cannabis, alcohol	-	-	-	-	-	-	-	-	-	-
DA49	S	SP	Antabuse	N.R.	-	-	-	-	-	-	-	-	-	-
DA50	A	ASPX	Heroin, OTC opioids	Heroin, methadone, amphetamines	-	-	-	-	-	BL	-	-	-	-

Table 2

Establishing a case history from Medical Examiner documents and next-of-kin interviews

	Medical Examiner	Autopsy Questionnaire	Postmortem Substance Abuse Assessment	Toxicology	
CASE/Drug	**Use specifics**	**Use specifics**	**Use specifics**	**GENERAL**	**HAIR***
DA15	Depression		Probation (cocaine distribution)		
Alcohol	In past, heavy	Regular, social	25 yrs, daily, drank alone	**NIC, CAFF**	**N/A**
Cocaine	-	In past	In past, not crack-cocaine	**AMI, norAMI**	
Nicotine	-	> 10 yrs, heavy	-	**CBZP, norCBZP**	
Cannabis	-	-	In past		
DA18					
Cannabis	-	Occasional	10 yrs	**COC, BE, CE**	**COC, cTHC**
Nicotine	-	10 yrs	-	**EME, EEE, THC**	
Alcohol	-	-	Daily, social		
DA22		N/A	SA treatment		
Cocaine	Addiction	-	25 yrs, regular, on/off	**BE, EME**	**COC**
Heroin	N.S.	-	-	**MOR, COD**	
Methadone	N.S.	-	In past, 10 yrs	**MTD**	
Alcohol	-	-	20 yrs, social		
Cannabis	-	-	In past		
Diet pills	-	-	25 yrs		
Valium	-	-	Daily		
Vicodin	-	-	In past		
Percocet	-	-	In past		
DA34					
Alcohol	Regular	Denied	Acknowledged	**BE, EME, MOR**	**COC, MOR, 6AM, COD**
DA43		N/A			
Alcohol	-	-	Acknowledged	**CAFF, LC, DZP**	**N/A**
DA44	Depression ?	BPD			
Substance use	N.R.	Denied	Denied	**FEN, norFEN PTP, MEC SRT, desSRT**	**NEG***
DA45	Depression ?	Depression, ADD	DUI (alcohol, age 22), ADHD		
Alcohol	?	? (in past)	Bingeing (college), social	**N.D.**	**N/A**

	Medical Examiner	Autopsy Questionnaire	Postmortem Substance Abuse Assessment	Toxicology	
CASE/Drug	**Use specifics**	**Use specifics**	**Use specifics**	**GENERAL**	**HAIR***
DA46	Overdose Hx	Psychiatric problems Suicidal gestures, detox (9 days)	Detoxes, AA (4–5x), multiple car accidents medication-related seizures		
Morphine	N.S.	-	Regular	**MOR**	**MOR, COD**
Rx abuse	20 yrs	-	Soma, Percocet, “Rx abuse”	**MIR**	**OXYC**
Methadone	-	-	N.S.		
Alcohol	-	Binges	-		
DA47	Psychiatric care, detoxes NA consulted	SA detoxes	SA detoxes (4x/30 yrs), AA/NA consulted Poor anger management/coping skills, PTSD		
Alcohol	Alcohol seizures	22 yrs, heavy, daily	25 yrs, daily	**NIC, CAFF**	**cTHC**
Cannabis	In past	In past, not recent	Acknowledged		
Phencyclidine	N.S.	In past, 6 mo regular use	Psychiatric care (PCP-rel.)		
Hallucinogens	N.S.	In past			
Cocaine			Powder		
DA48	SCHIZ, depression	-	AA/NA consulted		
Alcohol	N.S.	Self-proclaimed alcoholic	Self-proclaimed alcoholic	**CIT**	**NEG***
Cannabis	-	-	In past (college years)		
DA49	SCHIZ	Mental illness (33 yrs)			
Antabuse	Rx	-	Denied	**THI, SAL**	**NEG***
DA50	Bulimia	Bulimia, depression	NA consulted, SA treatment		
Heroin	"Problems" (H.S.)	In past	In past, daily, 2 yrs	**DEXM, CHL**	**NEG***
Methadone	-	-	In past, 2 yrs		
Theraflu®	N.S.	-	-		
Amphetamines	-	In past	-		

*Hair testing examined the presence of COC, PCP, cTHC, amphetamines and opioids.

Comparison of case history provided by the Medical Examiner’s (ME) Office, the Autopsy Questionnaire (AQ), and the Postmortem Substance Abuse Assessment Questionnaire (PSAAQ). General toxicology includes all toxicology but excludes hair testing (listed separately). *Abbreviations:* 6AM – 6-acetyl morphine, AA – Alcoholics Anonymous, ADD - attention deficit disorder; ADHD – attention deficit hyperactivity disorder, AMI – amitriptyline, BE – benzoylecgonine, BPD –bipolar disorder, CAFF – caffeine, CBZP – cyclobenzaprine, CE – cocaethylene, CHL – chlorpheniramine, CIT –citalopram, COC – cocaine, COD – codeine, cTHC – 11-nor-9-carboxy-tetrahydrocannabinol, desSRT –desmethylsertraline, DEXM – dextromethorphan, DZP – diazepam, DUI – driving under the influence, EEE –ecgonine ethyl ester, EME – ecgonine methyl ester, FEN – fentanyl, H.S. – high school, Hx – history, LC – lidocaine, MEC– meclopramide, MIR – mirtazapine, MOR – morphine, MTD – methadone, NA – Narcotics Anonymous, N/A –not available, NEG – negative, NIC – nicotine, norAMI – noramitriptyline, norCBZP – norcyclobenzaprine, norFEN – norfentanyl, N.R. – nothing reported, N.S. – reported, nothing specified, OXYC – oxycodone, PCP – phencyclidine, PTP – protriptyline, PTSD – post-traumatic stress disorder, Rx – prescription drug, SA – substance abuse, SAL –salicylate, SCHIZ – schizophrenia, Soma – carisoprodol, SRT – sertraline, THC - delta-9-tetrahydrocannabinol, THI –thioridazine.

Table 3

Identification of substance use by source

Drug of abuse identified by	Medical Examiner (case history, toxicology)	Next-of-kin interviews	Total by case history	Toxicology (GTox, HT)	Total by case history and toxicology
Cocaine	**15 cases** (5, 11)	**11 cases**	**14 cases**	**30 cases** (15, 24)	**33 cases**
Cannabis	**11 cases** (7, 4)	**17 cases**	**22 cases**	**20 cases** (12, 18)	**29 cases**
Phencyclidine	**4 cases** (2, 3)	**1 case**	**2 cases**	**8 cases** (4, 5)	**10 cases**
Opioids	**4 cases** (3, 4)	**4 cases**	**4 cases**	**9 cases** (6, 6)	**9 cases**

Information on substance use was retrieved from the Medical Examiner (ME, by case history and toxicology, respectively), next-of-kin interviews, toxicology (by general toxicology (GTox, all toxicology excluding hair testing) and by hair testing (HT). Cases identified by case history encompass ME case history and next-of-kin interviews.

Table 4

Substance use identified by case history

Substance use identified by case history				
Corroborated by	**General toxicology**	**Hair testing**	**Toxicology Sensitivity**	**Toxicology Specificity**
Cocaine (14)	**50%** (7/14)	**82%** (9/11*)	**71%** (10/14)	**49%** (17/36)
Cannabis (22)	**32%** (7/22)	**64%** (14/22)	**64%** (14/22)	**75%** (21/28)
Phencyclidine (2)	**0%** (0/2)	**0%** (0/1*)	**0%** (0/2)	**83%** (40/48)
Opioids (4)	**75%** (3/4)	**33%** (1/3*)	**75%** (3/4)	**91%** (42/46)

Substance use cases identified via Medical Examiner case history and/or next-of-kin interviews were examined with respect to the corroboration by general toxicology (all toxicology excluding hair testing) and hair testing. Sensitivity and specificity measures of toxicology (general toxicology and hair testing) corroborating a specific substance use history were calculated for each drug of abuse. Sensitivity indicates the number of true positive cases (both by reference (case history) and by test) to all reference positive cases. Specificity indicates the number of true negative cases (by reference (case history) and by test) to all reference negative cases. Asterisks indicates that hair testing was not possible for all cases.

Table 5
Substance use identified by toxicology and by hair testing

Substance use	Identified by toxicology		Identified by hair testing			
Corroborated by	Case history		Case history		General toxicology	
Toxicology	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Cocaine	**40%** (12/30)	**85%** (17/20)	**38%** (9/24)	**85%** (11/13)	**42%** (10/24)	**92%** (12/13)
Cannabis	**64%** (14/22)	**75%** (21/28)	**79%** (15/19)	**72%** (13/18)	**53%** (10/19)	**100%** (18/18)
Phencyclidine	**0%** (0/7)	**95%** (41/43)	**0%** (0/5)	**100%** (32/32)	**20%** (1/5)	**99%** (31/32)
Opioids	**29%** (2/7)	**95%** (41/43)	**20%** (1/5)	**94%** (30/32)	**60%** (3/5)	**94%** (30/32)

Substance use cases were identified by toxicology (Medical Examiner, supplementary and hair testing) or solely by hair testing, and compared to case history and – for cases identified by hair testing – also to general toxicology to examine how well the toxicological data were corroborated by these. Hair testing was possible for 37/50 cases. For each drug of abuse, sensitivity and specificity was calculated with respect to the reference method (toxicology for the first two columns and hair testing for the latter four columns). Sensitivity indicates the number of true positive cases (both by reference and by test) to all reference positive cases. Specificity indicates the number of true negative cases (by reference and by test) to all reference negative cases.