National Association of Medical Examiners Position Paper: Recommendations for the Investigation, Diagnosis, and Certification of Deaths Related to Opioid Drugs

Gregory G. Davis MD MSPH and the National Association of Medical Examiners and American College of Medical Toxicology Expert Panel on Evaluating and Reporting Opioid Deaths

ABSTRACT: The American College of Medical Toxicology and the National Association of Medical Examiners convened an expert panel to generate evidence-based recommendations for the practice of death investigation and autopsy, toxicological analysis, interpretation of toxicology findings, and death certification to improve the precision of death certificate data available for public health surveillance. The panel finds the following:

1. A complete autopsy is necessary for optimal interpretation of toxicology results, which must also be considered in the context of the circumstances surrounding death, medical history, and scene findings.
2. A complete scene investigation extends to reconciliation of prescription information and pill counts.
3. Blood, urine, and vitreous humor, when available, should be retained in all cases. Blood from the femoral vein is preferable to blood from other sites.
4. A toxicological panel should be comprehensive and include opioid and benzodiazepine analytes, as well as other potent depressant, stimulant, and anti-depressant medications.
5. Interpretation of postmortem opioid concentrations requires correlation with medical history, scene investigation, and autopsy findings.
6. If death is attributed to any drug or combination of drugs (whether as cause or contributing factor), the certifier should list all the responsible substances by generic name in the autopsy report and on the death certificate.
7. The best classification for manner of death in deaths due to the misuse or abuse of opioids without any apparent intent of self-harm is “accident.” Reserve “undetermined” as the manner for the rare cases in which evidence exists to support more than one possible determination.

KEYWORDS: Forensic pathology, Forensic toxicology, Medical toxicology, Opioid, Opiate, Death certification, Autopsy, Drug abuse, Surveillance, Public health

Gregory G. Davis MD MSPH is an Associate Coroner/Medical Examiner at the Jefferson County Coroner/Medical Examiner Office and a Professor of Pathology at the University of Alabama at Birmingham.

Contact Dr. Davis at: gdavis@uab.edu.

Acad Forensic Pathol
2013 3 (1): 77-83

INTRODUCTION

The term “opioid” in this document refers to any substance that stimulates the body’s opioid receptors, whether that substance is naturally derived (e.g., morphine, codeine), semisynthetic (e.g., hydrocodone, oxycodone), or synthetic (e.g., methadone, fentanyl). Opioids marketed for pain relief are called opioid analgesics (1). Since 1999, the number of intoxication deaths involving opioid analgesics in the United States has quadrupled (2). In 2012, the American College of Medical Toxicology (ACMT) and the National Association of Medical Examiners

(NAME), with financial support provided by the Centers for Disease Control and Prevention (CDC), convened an expert panel consisting of pathologists and toxicologists to address death investigation and certification of opioid drug related deaths. This panel systematically reviewed the peer-reviewed literature regarding the topic of fatal opioid analgesic poisoning. The intent of this panel was to develop evidence-based recommendations for the practice of death investigation and autopsy, toxicological analysis, interpretation of those analyses, and death certification in order to better inform public health surveillance and epidemiologic efforts. The panel formulated six questions designed to address best practices and searched the literature to provide evidence to support those practices. Details of the development of the questions, the level of evidence available in the medical literature, and the supporting data are provided in a companion article (3); this article provides a summary of the panel's recommendations.

1. Within the bounds of state law, which deaths require assumption of jurisdiction and performance of an autopsy?

Because autopsy provides the most accurate means of determining the cause of death (4), the panel recommends that a medical examiner or coroner (ME/C) assume jurisdiction and perform an autopsy to determine the cause and manner of death whenever intoxication is suspected as a possible cause for death. NAME also recommends that an autopsy be performed whenever intoxication is suspected (5). The panel further recommends that a ME/C office receive sufficient funding and personnel to meet this standard. Local laws governing jurisdiction might also influence which cases receive autopsies (5). The panel recognizes that some drug abusers are infected with blood-borne pathogens (e.g., Hepatitis C or Human Immunodeficiency Virus) (6), but proper precautions allow those performing the autopsy and toxicological analysis to minimize the risk of infection (7). Therefore, concern regarding contracting an infectious disease while performing an autopsy in these cases is an inadequate reason to avoid internal autopsy examinations. External examination is an inadequate substitute for autopsy for the purposes of detecting and certifying drug caused deaths. The panel recommends that whenever a ME/C assumes jurisdiction in a death, the ME/C should also seek and assume jurisdiction over any laboratory specimens, such as blood, serum and urine, obtained prior to death by medical professionals (8).

2. What constitutes appropriate and necessary scene investigation?

The expert panel supports the practices recommended in the *USDOJ National Institute of Justice (NIJ) Death Investigation Guidelines* published by the United States Department of Justice (9). The panel concurs with the investigative guidelines calling for an investigator and ME/C to look for evidence of drug use, misuse, or abuse; examples are listed in **Table 1**. The ME/C should document any medical therapy, both at the scene in the form of acute resuscitation attempts (e.g., intravenous access sites, naloxone administration) and subsequently in the form of medical and prescription records concerning the decedent's medical history.

Table 1: Examples of Scene Findings Suggesting Opioid Misuse or Abuse

Opioid medications
History of methadone use
Evidence of intravenous drug abuse (needles, cooker spoons, tourniquet, crushed tablets, packets of powder or crystals, other drug paraphernalia)
Overlapping prescriptions for the same type of prescribed controlled substances, prescriptions for controlled substances from multiple pharmacies or multiple prescribers
Prescriptions in other people's names
Pills not stored in prescription vials or mixed in vials
Injection sites not due to resuscitation attempts
Altered transdermal patches
Many transdermal patches on body or transdermal patches in unusual locations, e.g., mouth, stomach, vagina, or rectum
Application of heat to increase the rate of transfer of drug from transdermal patch to decedent
Presence of naloxone

The panel recommends taking an inventory of all medications found at the scene. If possible, seek information from state prescription drug monitoring programs, which have information that can be useful in the evaluation of deaths where opioid drugs are detected. For this reason, the panel recommends that ME/Cs have access to the information available in prescription drug monitoring programs both in the decedent's state and across state lines.

3. When is it appropriate or necessary to perform toxicology testing?

The combination of history, investigative information, and autopsy is an insensitive indicator of drug intoxication (10, 11), but constraints on resources are common in forensic practice. Some forensic offices have found it useful to assess cases in the morgue for the presence of drugs based on a quick screening test of urine with a kit (11, 12). Screening tests alone offer only weak evidence, are subject to false negatives, and are inadequate for establishing a cause of death (11, 12). Therefore, the panel recommends performing toxicological analysis for controlled substances on all decedents for whom one or more of the following circumstances are true:

1. *Known history of prescription opioid or illicit drug use, misuse, or abuse (13);*

2. *Evidence of opioid or illicit drug abuse revealed by scene investigation;*

3. *Autopsy findings suggesting a history of illicit drug abuse (including needle marks, hepatic cirrhosis, and cases in which birefringent crystalline material is within foreign body giant cells in the lungs);*

4. *Massive lung edema and froth in airways present with no grossly visible explanation (e.g., heart disease) or other non-toxicological explanation (e.g., epileptic seizure) (14);*

5. *Potential or suspected smugglers of illicit drugs (mules) (15);*

6. *No unequivocal cause for death identified at autopsy;*

7. *Decedents with a potential natural cause of death visible at autopsy whenever a drug may have precipitated or contributed to death by an additive mechanism, such as opioid-induced respiratory depression; or*

8. *Traumatic deaths.*

4. What are the best techniques for specimen collection and what should be the scope of the toxicological analysis?

Factors such as delay in autopsy, sampling technique, and specimen preservation contribute more to inaccuracies associated with toxicological testing than do the testing procedures themselves (16), but procuring and storing toxicology specimens under optimal conditions mitigate these factors (8, 17). The NAME standards call for collection of blood, urine, and vitreous humor as toxicology specimens in all cases whenever these specimens are available (5). Specimens that may be particularly relevant to deaths related to opioids include blood, vitreous humor, urine, bile, and gastric contents.

Because of postmortem redistribution of drugs, the best source of a blood sample for toxicological analysis is the ilio-femoral vein (8, 17). Although some ME/Cs ligate the femoral vein and draw distal to the ligation under direct visualization, at least one study shows that samples drawn by blind stick access to the femoral vein yield closely comparable concentrations (18). If femoral vein blood is not available, then blood from the subclavian vein, the right atrium of the heart, or any other intact blood vessel is the next choice, listed in decreasing order of desirability (8). Blood obtained from a body cavity is a specimen of last resort.

Label each specimen as accurately as possible regarding the anatomical source of the specimen (e.g., "blood from femoral vein", not "blood"). Store specimens in tightly sealed containers at 4° C for short-term storage. Sodium oxalate and sodium fluoride are the anticoagulant and preservative, respectively, of choice for blood for routine cases. Articles summarize and detail specimen selection, collection, and storage (8, 17).

An adequate analyte panel for opioid substances includes all common opioid analytes, including but not necessarily limited to those listed below:

Buprenorphine
Codeine
Fentanyl
Hydrocodone
Hydromorphone
Meperidine
Methadone
6-Acetylmorphine
Morphine
Oxycodone
Oxymorphone
Propoxyphene
Tapentadol
Tramadol

An analyte panel should also include other medications such as:

Benzodiazepines
Antidepressants
Muscle relaxants
Sleep aids
Ethanol
Stimulants (e.g., cocaine and amphetamines)

This list will change over time as pharmaceutical companies market new drugs or cease production of a drug that is currently available.

5. How does the interpretation of postmortem drug concentrations affect the certification of deaths related to opioids?

Postmortem drug concentrations are useful, even essential, in the determination of cause of death, but toxicological test results must be interpreted in the context of the circumstances surrounding death, the medical history, the scene of the death, and the autopsy findings (19, 20). A ME/C must use caution when relying on case studies and published tables of toxicology results, which are often based on a few cases and provide little or no contextual information about specific case details. Given the proper circumstances and autopsy findings, a drug can cause death even at a concentration below what some consider a reported lethal range. Conversely, the simple presence of a drug concentration within the reported lethal range does not necessarily make the drug the cause of death. Drug concentrations measured in postmortem samples cannot be used to reliably calculate the precise quantity of medication consumed (21).

Postmortem redistribution (PMR) is unpredictable in magnitude and direction and may not occur in every case. Nevertheless, a ME/C can generally make reasoned, clear, and defensible determinations of the cause and manner of death by using sound judgment based on the complete investigative and autopsy findings. The existence of PMR should not serve as an excuse to avoid making decisions concerning cause and manner of death in cases with toxicological findings.

Tolerance accounts for some of the overlap between therapeutic, supratherapeutic, and lethal concentrations of opioid analgesics observed in decedents, complicating the interpretation of postmortem concentrations of opioids and other drugs (22). There is no reliable quantifiable measure of drug tolerance before or after death.

Drug-drug or drug-toxicant interactions are complex and can occur on two levels – pharmacokinetic and pharmacodynamic (23). Because many variables determine whether any interactions occur, no *a priori* method can determine whether any interaction occurred in a given case; this should not, however, preclude consideration of potential interactions with respect to cause of death determination.

Determination of the cause of death should account for pathways of drug metabolism. Given that heroin is metabolized rapidly to 6-acetylmorphine (6-AM), the presence of 6-AM rather than heroin is sufficient to ascribe intoxication to heroin. In the absence of 6-AM, heroin use can be reasonably inferred by other means. For example, pure morphine could come from the ingestion of morphine or as a metabolite of codeine. In heroin, however, codeine from the opium derived from poppies is present as a slight contaminant, and so a morphine:codeine ratio greater than 1 may be considered as evidence of heroin use (24, 25).

Interpretation of solid tissue concentrations of drugs is complicated and often impossible beyond qualitative evidence of exposure. Drugs may distribute unevenly throughout organs such as the liver or brain because of variations in blood flow, bio-accumulation, and other factors, further complicating interpretation (26).

6. What are the optimal methods for determining and recording (certifying) cause of death, manner of death, and how injury occurred (including wording on the death certificate)?

Death certificate data are often used to determine priorities in public health. Four sections of the death certificate are particularly important to research and public health work on opioid-related deaths: Cause of Death, Other Significant Conditions Contributing to Death, Manner of Death, and the section labeled "Describe How Injury Occurred." Death certificates must be completed and filed as soon as possible following death, and completion is sometimes necessary before toxicology results become available. Nevertheless, in order to maximize useful information about opioid drug deaths, the panel recommends that the death certificate be completed with the most specific details available about a given death and amended when pending results return.

Cause of Death

If a death is attributed to a single drug or to a combination of drugs, whether as cause or as a contributing factor, then the best and recom-

mended practice is to list the generic name of all of the chemical agents that the pathologist considers responsible for causing death in the autopsy report and on the death certificate (27, 28). The recommended approach applies to drugs present in concentrations sufficient to have caused death or contributed to death in a given case. Avoid vague, nonspecific descriptions such as "mixed drug intoxication" or "polypharmacy."

Other Significant Conditions

In this section, also referred to as "Part II" of the Cause of Death, list conditions that might have predisposed the person to death but which were neither necessary nor sufficient to cause death. For example, obstructive sleep apnea might contribute to death from an opioid overdose without being the underlying cause of death. The recommendations for specificity in wording the cause of death also apply to listing contributing factors.

Manner of Death

Drug-related deaths are often complex, requiring thorough investigation. This investigative information is then used in conjunction with the results of the autopsy and toxicological testing to determine a manner of death, whether accident, suicide, or homicide. The determination of suicide is often difficult; ME/Cs must base a determination of suicide on appropriate investigative information and postmortem findings and be able to defend this determination. Published guidelines from the CDC indicate that in a suicide the fatal injury must be consistent with being self-inflicted and that there should be indication of intent of self-harm (28, 29). By these criteria, intentional misuse of opioids in excess amounts for self-treatment or for the sensations that the drugs cause, while dangerous, does not by itself constitute a suicide. At the same time, assigning "undetermined" as the manner of death as a matter of course for deaths due to intoxication does not serve the public good, nor does this practice support efforts to intervene and prevent future intoxication deaths of a similar sort. The panel recommends classifying deaths from the misuse or abuse of opioids without any apparent intent of self-harm as "accident." Reserve "undetermined" as the manner for the rare cases in which evidence exists to support more than one possible determination, that is, where some evidence suggests accident and other evidence suggests suicide or homicide.

How Injury Occurred

The drugs to which fatal intoxication is attributed should be listed in the "Cause of Death" field. The "How Injury Occurred" field should include the known information about the history, route of administration, drug source, and the type of drug formulation, as shown in **Table 2**. Examples for "How Injury Occurred" might include: "history of chronic back pain, ingested drug prescribed to decedent" or "injected illicit substance." While it is true that more specific information is preferable to general statements, avoid the use of personal identifiers in this section, as such information may impede attempts to create de-identified data for public health work and may later prove to be incorrect.

SUMMARY

The recommendations of this panel are based on the best evidence provided in the medical literature for the investigation, evaluation, and certification of opioid-related deaths at the time of review. Additional detail concerning these recommendations is available in a companion paper (3). ME/Cs and toxicologists value their ability to work independently, but cooperation on a problem common to all strengthens the ME/C community's response to the opioid epidemic. Use of these recommendations will improve the detection and reporting of opioid-related deaths. Improved surveillance will reveal the magnitude of opioid-related deaths more accurately, thus clarifying attempts to decrease the number of opioid-related deaths and improving public health by monitoring the effects of these interventions.

Table 2: Useful Information for "How Injury Occurred"

Information	Examples of Details
Medical history	History of chronic pain, origin of pain (e.g., motor vehicle accident, fall, cancer), history or evidence of drug use, abuse or misuse (e.g., intravenous abuse, prescription medication abuse, methadone treatment, detoxification admissions)
Route of administration	Oral ingestion, intravenous injection, snorted, smoked, transdermal, transmucosal, unknown
Source of drug	Prescription, illicit street purchase, diverted from another person's prescription, unknown source
Type of formulation	Long-acting or extended release opioid, immediate-release opioid

AUTHORS

Lead Author:
Gregory G. Davis MD MSPH

Opioid Panel:
Lewis S. Nelson MD – Chair
Sally S. Aiken MD
Gregory G. Davis MD MSPH
Henrik Druid MD PhD
James R. Gill MD
Bruce A. Goldberger PhD
Judy Melinek MD
Robert A. Middleberg PhD
Owen L. Middleton MD
Jeanmarie Perrone MD
Paul M. Wax MD
Kurt B. Nolte MD – Principal Investigator

Review Consultants:
Edward W. Boyer PhD MD
Gregory J. Davis MD
Corinne L. Fligner MD
Chris Gharibo MD
Stacey Hail MD
Daliah Heller PhD MPH
Jacqueline Martin MD
Denise Paone EdD BSN
Agnieszka Rogalska MD

Information Management Consultant:
Gale G. Hannigan PhD MPH

ACKNOWLEDGEMENTS

The panelists gratefully acknowledge the technical support and expertise that librarians Gale Hannigan and Brian Bunnett of the University of New Mexico Health Sciences Library provided by searching the literature, gathering articles, checking citations and recording the outcome of the review process. In addition, the panelists are thankful for the assistance of Denise McNally of the National Association of Medical Examiners for facilitating the multiple conference calls required to produce the final document.

DISCLOSURES

Funding support for this project was received from the Centers for Disease Control and Prevention (CDC), contract number 00HCUD3-2011-99784. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC. Drs Aiken, Greg G. Davis, Gill, Goldberger, Melinek, Middleberg, Middleton, Nelson, Perrone and Wax received travel funds from the CDC award to participate in the expert panels. Drs Goldberger and Middleberg received honoraria for their participation in the expert panel. Drs Boyer, Gill, Melinek, Nelson and Goldberger have received fees to be expert consultants and provide testimony in legal matters. Drs Gharibo and Gill have received payments for lectures. Dr. Gill has received royalties from the publication of scientific books and the development of a Medicolegal course. Dr. Middleberg is employed by the NMS laboratory which has done fee-for-service work for the CDC. Dr. Nolte's institution, the New Mexico Office of the Medical Investigator, received funds from the CDC to support the creation of this paper including his role as principal investigator and receives funds from the National Association of Medical Examiners (NAME) to support his role as Executive Vice President. In addition, Dr. Nolte's institution has research awards in which he participates from the National Institute of Justice and National Institutes of Health (through Portland State University). Dr. Wax receives funds from the American College of Medical Toxicologists to be the Executive Director.

The opinions and conclusions of this paper have been reviewed and approved by the National Association of Medical Examiners Board of Directors and as such are endorsed by NAME. These opinions and positions are based on a consensus of the current literature, knowledge, and prevailing theories on this topic. As Scientific knowledge and experience grow, NAME reserves the right to revise or update these opinions. The process by which NAME position papers are initiated, written, reviewed, and approved is publically available at https://netforum.avectra.com/temp/ClientImages/NAME/2c26a527-f992-4f70-9d03-7941bff5319d.pdf. All scientific position papers endorsed by the National Association of Medical Examiners automatically expire five years after publication unless reaffirmed, revised, or retired at or before that time. This work is a product of NAME and as such, was not subjected to *Academic Forensic Pathology Journal* editorial review.

The editors and publication staff do not report any relevant conflicts of interest.

REFERENCES

1) Yaksh TL, Wallace MS: Opioids, Analgesia, and Pain Management. In: Brunton LL, Chabner BA, Knollmann BC, eds: Goodman & Gilman's The pharmacological basis of therapeutics, 12th ed. New York: The McGraw-Hill Companies, Inc., 2011:481-525.

2) CDC 24/7: Saving lives. Protecting people [Internet]. Atlanta: Centers for Disease Control and Prevention; c2011. Morbidity and Mortality Weekly Report (MMWR) November 4, 2011; 60(43); 1487-92. Vital Signs: Overdoses of Prescription Opioid Pain Relievers — United States, 1999–2008; 2011 Nov 4

[cited 2013 Jan 16]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm.

3) Davis GG, National Association of Medical Examiners and American College of Medical Toxicology Expert Panel on Evaluating and Reporting Opioid Deaths. Recommendations for the investigation, diagnosis, and certification of deaths related to opioid drugs. *Acad Forensic Pathol*. 2013 Mar; 3(1):62-76.

4) Nashelsky MB, Lawrence CH. Accuracy of cause of death determination without forensic autopsy examination. *Am J Forensic Med Pathol*. 2003 Dec; 24(4):313-9.

5) Forensic Autopsy Performance Standards; 2011 revision [Internet]. Marceline (MO): National Association of Medical Examiners; 2011 Aug 11 [cited 2013 Jan 16]. 27 p. Available from: http://thename.org/index2.php?option=com_docman&task=doc_view&gid=160&Itemid=26.

6) Burt RD, Hagan H, Garfein RS, et al. Trends in hepatitis B virus, hepatitis C virus, and human immunodeficiency virus prevalence, risk behaviors, and preventive measures among Seattle injection drug users aged 18-30 years, 1994-2004. *J Urban Health*. 2007 May; 84(3):436-54.

7) Nolte KB, Taylor DG, Richmond JY. Biosafety considerations for autopsy. *Am J Forensic Med Pathol*. 2002 Jun; 23(2):107-22.

8) Dinis-Oliveira RJ, Carvalho F, Duarte JA, et al. Collection of biological samples in forensic toxicology. *Toxicol Mech Methods*. 2010 Sep; 20(7):363-414.

9) U.S. National Institute of Justice, Office of Justice Programs [Internet]. Washington: the Institute; [updated 2011 Jun]. Death Investigation: A Guide for the Scene Investigator [updated 2011 Jun; cited 2013 Jan 16]. Available from: http://www.nij.gov/pubs-sum/234457.htm.

10) Gruszecki AC, Booth J, Davis GG. The predictive value of history and scene investigation for toxicology results in a medical examiner population. *Am J Forensic Med Pathol*. 2007 Jun; 28(2):103-6.

11) Ceelen M, Dorn T, Buster M, et al. Post-mortem toxicological urine screening in cause of death determination. *Hum Exp Toxicol*. 2011 Sep; 30(9):1165-73.

12) Cina SJ, Collins KA, Goldberger BA. Toxicology: What is routine for medicolegal death investigation purposes? *Acad Forensic Pathol*. 2011 Jul; 1(1):28-31.

13) Poulin C, Stein J, Butt J. Surveillance of drug overdose deaths using medical examiner data. *Chronic Dis Can*. 1998; 19(4):177-82.

14) Dinis-Oliveira RJ, Santos A, Magalhães T. "Foam Cone" exuding from the mouth and nostrils following heroin overdose. *Toxicol Mech Methods*. 2012 Feb; 22(2):159-60.

15) Gill JR, Graham SM. Ten years of "body packers" in New York City: 50 deaths. *J Forensic Sci*. 2002 Jul; 47(4):843-6.

16) Linnet K, Johansen SS, Buchard A, et al. Dominance of pre-analytical over analytical variation for the measurement of methadone and its main metabolite in postmortem femoral blood. *Forensic Sci Int*. 2008 Jul 18; 179(1):78-82.

17) Skopp G. Preanalytic aspects in postmortem toxicology. *Forensic Sci Int*. 2004 Jun 10; 142(2-3):75-100.

18) Hargrove VM, McCutcheon JR. Comparison of drug concentrations taken from clamped and unclamped femoral vessels. *J Anal Toxicol*. 2008 Oct; 32(8):621-5.

19) Thompson JG, Vanderwerf S, Seningen J, et al. Free oxycodone concentrations in 67 postmortem cases from the Hennepin County Medical Examiner's Office. *J Anal Toxicol*. 2008 Oct; 32(8):673-9.

20) Andresen H, Gullans A, Veselinovic M, et al. Fentanyl: toxic or therapeutic? Postmortem and antemortem blood concentrations after transdermal fentanyl application. *J Anal Toxicol*. 2012 Apr; 36(3):182-94.

21) Cook DS, Braithwaite RA, Hale RA. Estimating antemortem drug concentrations from postmortem blood samples: the influence of postmortem redistribution. *J Clin Pathol*. 2000 Apr; 53(4):282-5.

22) Ferner RE. Post-mortem clinical pharmacology. *Br J Clin Pharmacol*. 2008 Oct; 66(4):430-43.

23) Pleuvry, BJ. Pharmacodynamic and pharmacokinetic drug interactions. *Anaesth & Intensive Care Med*. 2005;6(4):129-33.

24) Ceder G, Jones AW. Concentration ratios of morphine to codeine in blood of impaired drivers as evidence of heroin use and not medication with codeine. *Clin Chem*. 2001 Nov; 47(11):1980-4.

25) Jones AW, Holmgren A. Concentration ratios of free-morphine to free-codeine in femoral blood in heroin-related poisoning deaths. *Leg Med (Tokyo)*. 2011 Jul; 13(4):171-3.

26) Madras BK, Kaufman MJ. Cocaine accumulation in dopamine-rich regions of the brain after i.v. administration: comparison with mazindol distribution. *Synapse*. 1994 Nov; 18(3):261-75.

27) Cone EJ, Fant RV, Rohay JM, et al. Oxycodone involvement in drug abuse deaths. II: Evidence for toxic multiple drug-drug interactions. *J Anal Toxicol*. 2004 Oct;28(7):616-24.

28) National Center for Health Statistics. Medical examiners' and coroners' handbook on death registration and fetal death reporting. Hyattsville, MD: Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2003 [cited 2013 Jan 26]. Available from: http://www.cdc.gov/nchs/data/misc/hb_me.pdf.

29) Rosenberg ML, Davidson LE, Smith JC, et al. Operational criteria for the determination of suicide. *J Forensic Sci*. 1988 Nov; 33(6):1445-56.