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15444 Chinnereth Est, Savannah, MO 64485
660-734-1891 Email: name@thename.org Website: www.thename.org

Recommendations for the Investigation, Diagnosis, and Certification of Deaths Related to Opioid and Other Drugs

December 17, 2019 – December 17, 2024 (Renewed until 2029)

Position Paper: **Recommendations for the Investigation, Diagnosis, and Certification of Deaths Related to Opioid and Other Drugs**

National Association of Medical Examiners Expert Panel on Evaluating and Reporting Opioid and Other Drug Deaths

Authors
Gregory G. Davis
Amy B. Cadwallader
Corinne L. Fligner
Thomas Gilson
Emma Hall
Kent Harshbarger
Robert Kronstrand
Craig Mallak
Jerri McLemore
Robert A. Middleberg
Owen L. Middleton
Lewis S. Nelson
Agnieszka Rogalska
Eric Tonsfeldt
Jeff Walterscheid
Ruth E. Winecker

Opioid Panel
Gregory G. Davis, MD, MSPH, chair
Amy B. Cadwallader, PhD
Corinne L. Fligner, MD
Thomas Gilson, MD
Emma Hall
Kent Harshbarger, MD, JD, MBA
Robert Kronstrand, PhD
Craig Mallak, MD, JD
Jerri McLemore, MD
Robert A. Middleberg, PhD
Owen L. Middleton, MD
Lewis S. Nelson, MD
Agnieszka Rogalska, MD
Eric Tonsfeldt

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Jeff Walterscheid, PhD
Ruth Winecker, PhD

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Bruce A. Goldberger, PhD
Nicole Jones, MS
Denise M^{c}Nally
Margaret Warner, PhD
Julie K. O'Donnell, PhD

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Abstract

The National Association of Medical Examiners convened an expert panel to update the Association's evidence-based recommendations for investigating and certifying deaths associated with opioids and other misused substances to improve death certificate and mortality data for public health surveillance. The recommendations are:

1. Autopsy provides the best information about a decedent's medical condition for optimal interpretation of toxicology results, circumstances surrounding death, medical history, and scene findings. The panel considers autopsy an essential component of investigating apparent overdose deaths.
2. Scene investigation includes reconciling prescription information and medication counts. Investigators should note drug paraphernalia or other evidence of using intoxicating substances.
3. Retain blood, urine, and vitreous humor whenever available. Blood from the ilio-femoral vein is preferable to blood from more central sites.
4. A toxicological panel should be comprehensive, including potent depressant, stimulant, and antidepressant medications. Detecting novel substances present in the community may require special testing.
5. When death is attributed to a drug or combination of drugs (as cause or contributing factor), the certifier should list the drugs by generic name in the autopsy report and death certificate.
6. The best classification for manner of death in an overdose without any apparent intent of self-harm is "accident."

Key words: forensic pathology, forensic toxicology, opioid, opiate, death certification, autopsy, drug misuse, surveillance, public health

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Introduction

In 2014, the National Association of Medical Examiners (NAME) and the American College of Medical Toxicology (ACMT) published a joint position paper of recommendations for the investigation, diagnosis, and certification of deaths related to opioids.[1] (Throughout this document the term "opioid" refers to any substance that stimulates the body's opioid receptors, whether that substance is naturally-derived, semisynthetic, or synthetic.) The Centers for Disease Control and Prevention (CDC) provided financial support that allowed an expert panel of pathologists and toxicologists to meet and address death investigation and certification of opioid-related deaths. The panel worked through 2013 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. That panel's work led to the paper approved by each organization and published in 2014.

The 2014 Position Paper accomplished its goal of providing evidence-based recommendations, shown through death certificate data by improved specificity for drugs causing overdose deaths following publication of the paper. The specificity for drugs causing death rose from 75% of certified overdose deaths in 2012 to 88% in 2017.[2] This improvement led the CDC to support an update of the position paper now that the 2014 position paper has sunsetted in accordance with NAME policy.[3]

Deaths from overdose continued to increase from 2014 (47,055 deaths)[4] to 2017 (70,237 deaths). Provisional data for 2018 show a 4% decrease from 2017, but the number of deaths from overdose in 2018 still exceeds deaths from overdose in 2014 by 44%.[5] While deaths involving a prescription opioid have declined, heroin deaths are holding steady and fentanyl deaths continue to increase. Meanwhile, deaths associated with stimulants such as cocaine or methamphetamine are increasing, often in combination with fentanyl. Novel illicit drugs such as fentanyl analogs and cathinone congeners are making toxicological identification of the specific drugs causing death more difficult. The need for careful surveillance for overdose deaths remains, and thus NAME, with the CDC's support, convened a new panel to review the 2014 position paper, the medical literature published in the interim, and the changing nature of drug deaths in the United States. This panel followed the same process that the first panel utilized and again responds to six questions designed to address investigation and certification of a suspected drug-related death. These responses constitute the best evidence-based practices at this time.

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

Autopsy provides the most accurate means of determining the cause of death.[6] Accordingly, NAME in its Forensic Autopsy Performance Standards continues to recommend autopsy as an integral part of investigating any death where intoxication is suspected of causing death.[7] Given

that the number of overdose deaths has tripled in the past two decades,[8] the number of deaths that require autopsy according to this standard of practice may be overwhelming for the resources of a death investigation office (personnel and budget). It would be convenient if some less intensive means of postmortem examination rivaled autopsy for accuracy, but the published evidence offers no substitute for autopsy. Studies published decade after decade show that autopsy provides the most sensitive and specific data to establish the factors that may have caused or contributed to death,[9,10,11] including the practice of forensic pathology. [6,12,13] External examination alone is less accurate than autopsy when drugs are present in the decedent,[14] even in the presence of scene findings that strongly suggest overdose as a possibility.[15] Postmortem radiology imaging, such as computed tomography scans, seems to offer some promise, but the literature concerning virtual autopsy and overdose deaths is sparse. A few articles concentrate on prescription medication overdoses.[16-17] A general study describes the use of postmortem CT scans in Australia as an integral part of the preliminary case evaluation process, along with medical history, circumstances surrounding death, the external appearance of the body, and overnight toxicology screens.[18] The report indicates that this process has reduced the office autopsy rate from 62% to 47%, but the report goes on to state that postmortem CT scans are an adjunct to autopsy by predicting findings at autopsy.[18] A study of the role of postmortem CT in the investigation of intentional medication overdoses found that in most cases of confirmed overdose the CT images showed no diagnostic features, though in some cases a well-defined layer of radio-opaque material was visible along the gastric mucosa.[16] The authors of these studies do not mention the role of CT in overdose deaths involving illicit drug or substance misuse. One article reports a retrospective study of individuals that died of intoxication with heroin or methadone or both.[19] The bodies in the study group and control group were examined after death by both whole body CT imaging and by conventional autopsy. The authors report that the triad of cerebral edema, pulmonary edema, and bladder distention was 100% specific but only 26% sensitive for a death due to opioid intoxication when compared to the control group. Given the paucity of scientific studies on the use of postmortem CT and other enhanced imaging in the investigation of suspected overdose deaths, the panel finds that this modality is best considered experimental and not ready for application in routine forensic practice until more studies comparing autopsy with postmortem CT imaging are published.

Taking the factors discussed in the preceding paragraph into consideration, the panel continues to recommend that a medical examiner or coroner (ME/C) assume jurisdiction and perform, or cause to be performed, an autopsy to determine the cause and manner of death whenever intoxication is suspected as a possible cause for death (with one exception described below). Peer-reviewed articles showing evidence that external examination-only coupled with strong evidence of illicit drug use (such as a cooker spoon and syringe on a countertop) are just as accurate as autopsy in a similar type of death scene have not been published. Scientific articles have been published for decades showing that diagnoses will be in error when compared to an autopsy in up to 20-30% of cases,[6,8-13] and death investigation offices can provide more accurate

determinations of the cause of death in suspected overdoses as well as in other cases by performing autopsies in these cases.

In an ideal world every death investigation office would have the resources and personnel to investigate each death reported to the office with an autopsy, but not every office operates in ideal circumstances. This leaves an office in the difficult position of not autopsying bodies that are best evaluated with an autopsy or else exceeding the NAME standard for maximum number of autopsies (250) per pathologist per year.[7] Neither of these choices serves the public well. For the good of death investigation and for public health the panel strongly recommends that a ME/C office receive enough funding and personnel to allow for autopsy of these suspected overdose deaths without violating the NAME autopsy practice standards.

An autopsy includes external examination, and in a suspected overdose death the pathologist should look for signs of illicit drug use, such as needle marks or needle tracks or any drug evidence or paraphernalia in the decedent's clothing.[20] The internal examination includes examination of the organs in the torso, head, and neck, where a pathologist may find evidence such as drug evidence or patches in a body cavity, pulmonary edema, a distended bladder, brain swelling,[21] or birefringent foreign body material in the lungs.[22] The panel recommends that whenever a ME/C does assume jurisdiction in a death, the ME/C should also seek and assume custody of any laboratory specimens obtained prior to death by medical professionals (e.g. blood, serum, or urine).[23] A death investigation office will increase its chance of obtaining hospital specimens by developing collegial relationships with the appropriate health care laboratories.

Before proceeding to Question 2, it is important to note that the NAME Forensic Autopsy Performance Standards do allow for deferring autopsy in a select subset of suspected overdose cases, specifically delayed deaths due to overdose or suspected overdose.[7] The panel agrees with this practice for this subset of cases. Such cases still deserve postmortem investigation with review of the medical record from the time of hospital admission to death. In determining the contribution of substances detected by toxicological analysis, the pathologist should look for particular features in the hospital evaluation, such as antemortem drug screens, clinical course and diagnoses, and any CT scans that may show lack of any internal finding that could better explain death. It is important to seek any admission blood or urine that could be used for postmortem toxicological analysis.

Finally, death investigation is governed by individual state or local law, with many factors informing regional variations in practice. Local laws governing jurisdiction influence which cases receive autopsies.[7] Individual families or entire communities may object to autopsy due to the procedure's real or perceived inconsistency with their religious or cultural priorities. In some cases, this has led to a legal hearing before a judge.[24] Far preferable to settling such disagreements in court is to develop good professional relationships with representative faith leaders in the community of practice and to involve those leaders in the interview portion of investigations occurring in their communities. An informed and empathetic discussion with the family and a faith leader that the family respects will often allow the family and the death investigation office to reach an acceptable accord. One common misapprehension about the

forensic process is that a long delay will occur prior to interment (usually the delay is shorter than the family anticipates, and frequently the pathologist can adjust the timing of autopsy on a case-by-case basis). Another misunderstanding is that the pursuit of cause and manner of death is one of purely medical curiosity, when in fact the cause and manner of the certification will likely have bearing on the family's ensuing administrative needs. Families sometimes do not understand that the implication or exclusion of another person's involvement in the circumstances of the subject's death may depend on autopsy findings. In the event that the family and death investigation office cannot reach an agreement suitable to each party, then a judge may hear and decide the matter.[24-25] In the event of a court order prohibiting an autopsy, the pathologist may wish to explain to the judge that the death certificate will indicate that a court order prohibited autopsy, which may lead the judge to reconsider the order prohibiting autopsy.

2. What constitutes an appropriate and necessary scene investigation?

The expert panel continues to support the practices recommended in the *USDOJ NIJ Death Investigation Guidelines* published by the United States Department of Justice.[26] The panel concurs with the investigative guidelines calling for an investigator and ME/C to look for evidence of drug use or misuse; 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.

Powerful opioids such as carfentanil have created fear that individuals responding to and investigating a scene may be overcome and even die by accidentally inhaling or touching these extremely potent substances. Fortunately, this fear has proved to be more theoretical than practical. The members of the American College of Medical Toxicology have extensive experience evaluating individuals in the emergency setting, and their experience has shown that simple measures are adequate to protect responders. Nitrile gloves prevent dermal absorption, and N95 respirator masks provide sufficient protection in the rare event that drug particles are suspended in air. Shields to protect the eyes and mouth are appropriate if exposure from a splash is a concern. Paramedics or individuals working at a death scene should be trained to recognize the signs and symptoms of opioid intoxication and have naloxone readily available to administer if an individual shows objective signs of hypoventilation or a depressed level of consciousness. The ACMT has a full position statement on this subject.[27]

The 2019 Position Paper Panel recommends taking an inventory of medications found at the scene. There is a place for judgment in making such an inventory on the part of the responsible death investigation system. All substances that seem pertinent are worthy of inventory, but an office must develop its own policies concerning how diligently to search and where a search ends (that is, does the investigator inventory substances and medications found in the immediate vicinity of the decedent, in the room, in the entire house?). If possible, state prescription drug monitoring programs should be queried for information that can be useful in

the evaluation of deaths where opioids are detected. Prescription drug monitoring programs are an effective means of reducing prescription drug diversion and thus "safeguard public health and safety while supporting the legitimate use of controlled substances."[28] The panel recommends that ME/Cs have access to the information available in prescription drug monitoring programs. Given the ease of travel in the United States, access to the prescription drug monitoring programs in adjacent states is appropriate for death investigation offices.

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,[29-30] 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.[30-31] Screening tests alone offer generally incomplete evidence, are subject to false positives, lack confirmation, and are thus inadequate for establishing a cause of death.[30 -31] Therefore, the panel recommends performing toxicological analysis to identify and quantify controlled and illicit substances as well as appropriate novel illicit drugs on all decedents for whom one or more of the following circumstances are true:

1. Known history of prescription drug or illicit substance use; [32]
2. Evidence of opioid or illicit drug or substance use revealed by scene investigation;
3. Autopsy findings suggesting a history of illicit drug or substance use (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);[33]
5. Potential or suspected smugglers of illicit drugs (mules);[34]
6. No unequivocal cause for death identified at autopsy;
7. Decedents with a potential natural cause of death visible at autopsy whenever a drug or substance may also play a role in death, whether that substance may have precipitated death or contributed to death by an additive mechanism, such as prescription drug-induced respiratory depression or methamphetamine-induced cardiomegaly; or
8. Traumatic deaths (that is, deaths caused by something other than natural disease).

The panel makes this recommendation with the understanding that these are general guidelines. It is not possible to anticipate every possible scenario, and a death investigation office must develop its own guidelines and use its own judgment as it investigates each case on its own merits.

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

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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.[35] Pathologists can mitigate these factors by procuring and storing toxicology specimens under optimal conditions.[23,36] The NAME Forensic Autopsy Performance Standards call for collection of blood, urine, and vitreous humor as toxicology specimens in all cases whenever these specimens are available.[7] Specimens that may be particularly relevant to deaths related to opioids include blood, vitreous humor, urine, bile,[23,37] and gastric contents.

Because of postmortem redistribution of drugs, the best source of a blood sample for toxicological analysis is the ilio-femoral vein.[23,36] If ilio-femoral vein blood is not available, then blood from the subclavian vein, the heart or aorta, or any other intact blood vessel is the next choice, listed in decreasing order of desirability.[23] Blood obtained from a body cavity is a specimen of last resort.

Label each specimen as specifically as possible regarding the anatomical source of the specimen (e.g., "blood from iliac vein" or "blood obtained externally from femoral vein", not "blood"). Store specimens in tightly sealed containers at 4° C for short term storage. Potassium oxalate and sodium fluoride are the anticoagulant and preservative, respectively, of choice for blood for routine cases; these chemicals are present in commercially prepared gray top tubes. Articles summarize and detail specimen selection, collection, and storage.[23,36]

The introduction of variant forms of drugs into the illicit drug market has made it difficult for toxicology panels to keep up with the variety of substances being sold and consumed in 2019. Sharing data among death investigation offices, toxicology laboratories, law enforcement agencies, etc. may help all these groups keep abreast of the constant change in the illicit drug market. Keeping abreast of the types of drugs seen locally, including those on the illicit drug market, is necessary to ensure adequate coverage in toxicological analyses.

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

buprenorphine (norbuprenorphine)
codeine
fentanyl (and fentanyl analogs)
hydrocodone
hydromorphone
loperamide
methadone
6-acetylmorphine
morphine
oxycodone
oxymorphone
tapentadol

tramadol

A full toxicological panel should include substances such as
opioids,
benzodiazepines,
antidepressants,
muscle relaxants,
sleep aids,
ethanol,
pain adjunctive medications (e.g., gabapentinoids, select anticonvulsants, etc.),
stimulants, and
new psychoactive drugs that become prevalent

This list will change over time as pharmaceutical companies market new drugs or cease production of a drug that is currently available and as new illicit psychoactive drugs enter and leave the market. ME/C offices should have a policy to periodically review the scope of the toxicology panel that the office routinely requests for its cases.

5. How does the interpretation of postmortem drug concentrations affect the certification of deaths related to drugs or intoxicating substances?

Death investigation differs from clinical medical practice in the use of toxicological analysis. Clinicians caring for living patients treat symptoms empirically and have little practical use for analyses that may not be completed until days after the patient has recovered or died. Death investigation, on the other hand, can wait for toxicological tests that will definitively identify and quantify drugs and other chemical substances present in a decedent's body at the time of death. 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.[38-39]

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. Furthermore, drug concentrations measured in postmortem samples should not be used to calculate the quantity of medication consumed.[40-41]

Postmortem redistribution 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 postmortem redistribution 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.[42] There is no reliable quantifiable measure of drug tolerance before or after death. Nevertheless, pathologists able to enter and search a state's Prescription Drug Monitoring Program database have access to more data concerning an individual's use of opioids than was generally available prior to the creation of these prescription databases. Evidence of a history of prescription opioid use may allow a pathologist to infer some degree of opioid tolerance as opposed to a decedent's being opioid-naïve, remembering that such an inference makes assumptions about appropriate use of the prescription medication that may or may not be true.

Drug-drug interactions are complex and can occur on two levels – pharmacokinetic and pharmacodynamic.[43] 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 based on known pharmacological properties.

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 in a biological sample rather than heroin is sufficient evidence 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 blood morphine:codeine ratio greater than 1 may be considered as evidence of heroin use,[44-45] particularly in a setting where illicit drug paraphernalia suggests illicit drug use.[46] Of course, if testing of residue in a syringe at the scene should reveal heroin, then that is stronger evidence still of heroin use.

Interpretation of solid tissue concentrations of drugs is complicated and often impossible beyond qualitative evidence of exposure, particularly in a body that has passed beyond autolysis to a more advanced stage of decomposition. Drugs may distribute unevenly throughout organs such as the liver or brain because of variations in blood flow, bio-accumulation, solubility in fat or water, and other factors, further complicating interpretation.[47]

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 drug-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 filed in accordance with state statutes, and filing is sometimes necessary before toxicology results and cause are known. Nevertheless, in order to maximize useful information about drug deaths, the

panel recommends that the death certificate be completed with the most specific details available about a given death and amended when toxicological results are known and interpreted.

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 recommended practice is to list the generic name of all of the drugs.[48-49] The recommended approach applies to drugs present in concentrations sufficient to have caused death or to have contributed to death in a given case. Avoid vague, non-specific descriptions such as "mixed drug intoxication" or "polypharmacy" without including the names of the drugs responsible for causing death.

It is easy to state that the certifier should record the drug or drugs that caused death, but distinguishing substances that played a role in death from substances that simply happened to be present at the time of death is complex, with many factors to consider. Suppose that analysis revealed eight different substances in a decedent – alprazolam, 6-acetylmorphine, morphine, codeine, hydrocodone, ethanol, acetaminophen, and diphenhydramine. Choosing only 1 of these 8 substances seems inappropriate, but simply listing every substance also seems inappropriate, as low concentrations of acetaminophen are unlikely to be toxic. As stated earlier, toxicological test results must be interpreted in the context of the circumstances surrounding death, the medical history, the decedent's experience with drugs, the scene of the death, and the autopsy findings. Concentrations can help distinguish substances that played a crucial role in causing death from substances that seem unlikely to be responsible for death. Unfortunately, there is no simple way to definitively distinguish between lethal and sub-lethal concentrations for an individual decedent since many factors influence the concentration in postmortem sample (e.g. postmortem redistribution) and its impact on the individual (e.g. tolerance). Nevertheless, knowledge of human physiology and pharmacology can provide useful clues for making this determination. The panel recommends consulting with a forensic pathologist or toxicologist when difficult questions of interpretation arise, as pathologists and toxicologists have experience with postmortem casework.

Drugs can be divided into various classes based on their mechanism of pharmacologic action. Opioids (heroin, fentanyl, fentanyl-analogs, oxycodone, hydrocodone, methadone, etc.) depress the normal function of the central nervous system, including the drive to continue breathing. Drugs in the benzodiazepine family (e.g. diazepam, alprazolam, lorazepam, temazepam, etc.) also depress the normal function of the central nervous system, as do ethanol and barbiturates. If investigation into the circumstances surrounding death indicates that the decedent seemed drowsy or difficult to wake or developed loud snoring, then that scenario suggests that any drugs present that depress the normal function of the central nervous system were likely to have played a role in causing that death.[20]

Other drugs stimulate the central nervous system, such as cocaine, drugs in the amphetamine family (methamphetamine or other amphetamine drug forms such as 3,4-methylenedioxymethamphetamine or 3,4-methylenedioxyamphetamine, etc.), and cathinones. If investigation into the circumstances surrounding death indicates that the decedent seemed unusually frantic or complained of burning up, or if the decedent entered a frenzied state exhibiting unusual strength, then those scenarios suggest that any drugs present that stimulate the central nervous system as cocaine and amphetamines do were likely to have played a role in causing that death and should be listed as causing death.[50] The presence of contraction band

necrosis in the heart also suggests that one or more of these sympathetic nervous system stimulants played a role in death, particularly if death followed a sudden collapse.[22]

Because cocaine and amphetamines are cardiotoxic, they have the potential to cause a dysrhythmia, which can cause sudden collapse and death.[22] Methadone also has the potential to cause a dysrhythmia and sudden death because of its association with a particular dysrhythmia called torsades de pointes.[51] Consider these substances as potential causes for death if they are present on toxicological analysis and the history indicates a sudden collapse and death.

As initially stated, determining which drugs played a role in death is difficult, and it is not made any easier by some of the new drugs that have entered the illicit market. Kratom and other new psychoactive substances appear to have both stimulant and sedative aspects to their pharmacologic action, and more substances are being released illicitly that have never had their pharmacological properties in humans determined. It is reasonable to consider structurally similar compounds as having similar pharmacologic effects in the certification of deaths involving chemical analogs that have not as yet been studied as thoroughly as their better-characterized parent compounds. Whatever the circumstances surrounding death and whatever the substances detected by toxicological analysis, the goal for death certification is to record the drug or drugs that the certifier believed caused or contributed to death. In 2019, the CDC published a reference guide with examples for completing the death certificate for drug toxicity deaths.[52] The CDC instructs certifiers to list only the parent drug rather than all the drug metabolites that may be listed in a toxicology report. For the hypothetical example where 8 different substances were detected in a decedent mentioned above, the best approach is to certify that "heroin" played a role in causing death rather than listing "6-acetylmorphine" and "morphine" (heroin metabolites) and "codeine" (an opioid naturally present in opium poppies and thus in heroin). Finally, the order in which the drugs are listed makes little difference to the public health system. The important thing is to record the drugs responsible for causing death and not to record drugs that played no role in death.

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 the certifier does not consider sufficient to have caused death in this particular case. 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. It is inappropriate to list all substances detected on toxicological analysis in this section, just as it is inappropriate to list medical conditions that did not cause death, however interesting those substances or conditions may be. The information supplied on the death certificate should pertain to the death.

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.[49,53] 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 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.

It is important to note that a death certificate is a public health document designed to provide information to promote improved public health. A death certificate is no place for the legal system to try to arrange words and concepts in a way to help one side of a potential legal dispute gain an advantage over the other side in a court of law. In particular, "homicide" as a manner of death is not a legal charge, and therefore it makes no medical sense to certify a death as a "homicide" to help an attorney that anticipates bringing some sort of criminal charge of wrongful death in a given case. The legal system must bring legal charges according to its mandate, and it can do so regardless of the manner determination by the certifier. Homicide as the manner of death for a drug overdose should be reserved for an intentional exposure to inappropriately sedate or end the life of a specific individual as a kind of assault or poisoning.

How Injury Occurred

Public health research seeks trends or associations with a specific cause of death to help determine the type of programs that may help reverse practices leading to unnecessary deaths. It is for this reason that death certificates request information on how the injury occurred. On the other hand, relatives of decedents are often opposed to having sensitive information on a document that they must present publicly in tending to the decedent's affairs after death. Meanwhile, the certifier often knows few of the sorts of details that health departments wish to know about overdose deaths, such as route of administration or the source of the drug. To the extent possible, health departments hope that certifiers will provide information in the "How Injury Occurred" field concerning information about the decedent's medical history that directly pertains to the cause of death, the route of administration, the drug source, and the type of drug formulation. 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.

Where Injury Occurred

Death certificates require a certifier to describe where and when the injury occurred. This can be difficult or impossible with overdoses. No one but the decedent may know where the decedent used the drug, or the decedent may have used one drug in one location and another drug later in a separate location. If the place of substance use is not known, then it is appropriate to enter the place where the decedent became unresponsive or was found dead.[52]

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. 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.

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Table 1. Examples of scene findings suggesting opioid misuse.

1. Opioid medications
2. Evidence of intravenous drug use (needles, cooker spoons, tourniquet, crushed tablets, packets of powder or crystals, other drug paraphernalia)
3. Evidence of insufflation (chopped pills or residue, chopped lines, cuts on coffee table glass, cut straws or pen tubes, rolled bills, etc.)
4. Overlapping prescriptions for the same type of prescribed controlled substances, prescriptions for controlled substances from multiple pharmacies or multiple prescribers
5. Prescriptions in other people's names
6. Pills not stored in prescription vials or mixed in vials
7. Injection sites not due to resuscitation attempts
8. Altered transdermal patches
9. Many transdermal patches on the body or transdermal patches in unusual locations, e.g., mouth, stomach, vagina, or rectum
10. Application of heat to increase the rate of transfer of drug from transdermal patch to decedent
11. Presence of naloxone

Table 2. Useful information for "How Injury Occurred."

Information	Examples of details
Medical history	history of chronic pain, origin of pain (motor vehicle accident, fall, cancer), history or evidence of drug use or misuse (intravenous use, prescription medication misuse, methadone treatment, detoxification admissions)
Route of administration	oral ingestion, intravenous injection, subcutaneous injection, insufflated (snorted), smoked, transdermal, transmucosal, unknown
Source of drug	prescription, illicit purchase, diverted from another person's prescription, unknown source
Type of formulation	long-acting or extended release opioid, immediate-release opioid

References

[1] Davis GG, National Association of Medical Examiners and American College of Medical Toxicology Expert Panel on Evaluating and Reporting Opioid Deaths. National Association of Medical Examiners Position Paper: Recommendations for the investigation, diagnosis, and certification of deaths related to opioid drugs. Acad Forensic Pathol 2013;3(1):77-83. See also republication in J Med Toxicol 2014;10(1):100-6.
[2] Warner M, Hedegaard H. Identifying opioid overdose deaths using vital statistics data (editorial). Am J Public Health. 2018;108(12):1587-9. doi: 10.2105/AJPH.2018.304781.
[3] NAME Position Paper Guidelines. Available from https://www.thename.org/assets/docs/Position%20Paper%20Process%202015.pdf [cited 2019 October 14].
[4] Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in Drug and Opioid Overdose Deaths--United States, 2000-2014. MMWR Morb Mortal Wkly Rep. 2016;64(50-51):1378-82. doi: 10.15585/mmwr.mm6450a3.
[5] Provisional drug overdose death counts. Vital Statistics Rapid Release; 2019. Available from https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm [cited 2019 August 26].
[6] Nashelsky MB, Lawrence CH. Accuracy of cause of death determination without forensic autopsy examination. Am J Forensic Med Pathol. 2003;24(4):313-9.
[7] Forensic Autopsy Performance Standards. Marceline, MO National Association of Medical Examiners; 2006; 2011 revision 2011. 27 p.
[8] Drug overdose deaths in the United States, 1999-2017. NCHS Data Brief. 2018;No.329. Available from https://www.cdc.gov/nchs/products/databriefs/db329.htm [cited 2019 August 26].
[9] Cabot RC. Diagnostic pitfalls identified during a study of three thousand autopsies. J Am Med Assoc 1912; 59:2295-8.
[10] Lundberg GD, Voigt GE. Reliability of a presumptive diagnosis in sudden unexpected death in adults. The case for the autopsy. JAMA 1979;242:2328–30.
[11] Sarode VR, Datta BN, Banerjee AK, Banerjee CK, Joshi K, Bhusnurmath B, et al. Autopsy findings and clinical diagnoses: a review of 1,000 cases. Hum Pathol 1993;24:194–8.
[12] Asnaes S, Paaske F. Uncertainty of determining cause of death in medicolegal material without autopsy: an autopsy study. Forensic Sci Int. 1980;15:103-14.
[13] Vanatta PR, Petty CS. Limitations of the forensic external examination in determining the cause and manner of death. Hum Pathol 1987;18:170–4.
[14] Gill JR, Scordi-Bello IA. Natural, unexpected deaths: reliability of a presumptive diagnosis. J Forensic Sci. 2010;55(1):78-81. doi: 10.1111/j.1556-4029.2009.01227.x.
[15] Dye DW, McGwin G Jr, Atherton DS, McCleskey B, Davis GG. Correctly identifying deaths due to drug toxicity without a forensic autopsy. Am J Forensic Med Pathol 2019;40(2):99-101.
[16] Burke MP, O'Donnell C, Bassed R. The use of postmortem computed tomography in the diagnosis of intentional medication overdose. Forensic Sci Med Pathol. 2012 Sep;8(3):218-36. doi: 10.1007/s12024-011-9292-z. Epub 2011 Nov 19.
[17] Usui A, Kawasumi Y, Usui K, Ishizuka Y, Takahashi K, Funayama M, Saito H. Postmortem Computed Tomographic Analysis of Death Caused by Oral Drug Intoxication. Tohoku J Exp Med. 2017 Jul;242(3):183-192. doi: 10.1620/tjem.242.183.

[18] O'Donnell C. An image of sudden death: utility of routine postmortem computed tomography scanning in medico-legal autopsy practice. Diagnostic Histopathology 2010;16(12):552-5.
[19] Winklhofer S, Surer E, Ampanozi G, Ruder T, Stolzmann P, Elliott M, Oestreich A, Kraemer T, Thali M, Alkadhi H, Schweitzer W. Post-mortem whole body computed tomography of opioid (heroin and methadone) fatalities: frequent findings and comparison to autopsy. Eur Radiol 2014;24:1276–1282. DOI 10.1007/s00330-014-3128-7.
[20] Gill JR. From death to death certificate: what do the dead say? J Med Toxicol 2017;13:111-6. doi 10.1007/s13181-016-0551-y.
[21] Molina DK, Vance K, Coleman ML, Hargrove VM. Testing an age-old adage: can autopsy findings be of assistance in differentiating opioid versus cardiac deaths? J Forensic Sci 2019 Sep 4. doi: 10.1111/1556-4029.14174.
[22] Milroy CM, Parai JL. The histopathology of drugs of abuse. Histopathology 2011 DOI: 10.1111/j.1365-2559.2010.03728.x.
[23] Dinis-Oliveira RJ, Carvalho F, Duarte JA, Remiao F, Marques A, Santos A, et al. Collection of biological samples in forensic toxicology. Toxicol Mech Methods. 2010;20(7):363-414.
[24] Boglioli LR, Taff ML. Religious objection to autopsy. An ethical dilemma for medical examiners. Am J Forensic Med Pathol. 1990 Mar. 11(1):1-8.
[25] Beal SG, Burton EC. Collins KA ed. Religions and the Autopsy. (https://emedicine.medscape.com/article/1705993-overview#showall) [cited 2019 July 20].
[26] Death Investigation: A Guide for the Scene Investigator: Technical Update. Washington, DC: U.S. Dept. of Justice. Office of Justice Programs. National Institute of Justice; 2011. Available from: https://www.ncjrs.gov/pdffiles1/nij/234457.pdf. [cited 2019 August 26].
[27] ACMT and AACT Position Statement: Preventing Occupational Fentanyl and Fentanyl Analog Exposure to Emergency Responders. 2017. Available from https://www.acmt.net/_Library/Positions/Fentanyl_PPE_Emergency_Responders_.pdf. [cited 2019 August 26].
[28] Prescription Drug Monitoring Program and Medical Examiner/Coroner Meeting: Building Collaboration. Available from https://www.pdmpassist.org/pdf/Resources/PDMP_ME-C_Meeting_Summary_20190703_a.pdf [cited 2019 August 26].
[29]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;28(2):103-6.
[30] Ceelen M, Dorn T, Buster M, Stomp J, Zweipfenning P, Das K. Post-mortem toxicological urine screening in cause of death determination. Hum Exp Toxicol. 2011;30(9):1165-73.
[31] Cina SJ, Collins KA, Goldberger BA. Toxicology: What is routine for medicolegal death investigation purposes? Acad Forensic Pathol. 2011;1(1):28-31.
[32] Poulin C, Stein J, Butt J. Surveillance of drug overdose deaths using medical examiner data. Chronic Dis Can. 1998;19(4):177-82.
[33] Dinis-Oliveira RJ, Santos A, Magalhaes T. "Foam Cone" exuding from the mouth and nostrils following heroin overdose. Toxicol Mech Methods. 2012;22(2):159-60.
[34] Gill JR, Graham SM. Ten years of "body packers" in New York City: 50 deaths. J Forensic Sci. 2002;47(4):843-6.

[35] Linnet K, Johansen SS, Buchard A, Munkholm J, Morling N. Dominance of pre-analytical over analytical variation for measurement of methadone and its main metabolite in postmortem femoral blood. Forensic Sci Int. 2008;179(1):78-82.
[36] Skopp G. Preanalytic aspects in postmortem toxicology. Forensic Sci Int. 2004;142(2-3):75-100.
[37] Ferner RE, Aronson JK. The toxicological significance of post-mortem drug concentrations in bile. Clinical Toxicology 2018;56(1):7-14. doi: 10.1080/15563650.2017.1339886.
[38] Thompson JG, Vanderwerf S, Seningen J, Carr M, Kloss J, Apple FS. Free oxycodone concentrations in 67 postmortem cases from the Hennepin County medical examiner's office. J Anal Toxicol. 2008;32(8):673-9.
[39] Andresen H, Gullans A, Veselinovic M, Anders S, Schmoldt A, Iwersen-Bergmann S, et al. Fentanyl: toxic or therapeutic? Postmortem and antemortem blood concentrations after transdermal fentanyl application. J Anal Toxicol. 2012;36(3):182-94.
[40] Cook DS, Braithwaite RA, Hale KA. Estimating antemortem drug concentrations from postmortem blood samples: the influence of postmortem redistribution. J Clin Pathol. 2000;53(4):282-5.
[41] ANSI/ASB Best Practice Recommendation 037, First Edition 2019 Guidelines for Opinions and Testimony in Forensic Toxicology. Available from http://www.asbstandardsboard.org/wp-content/uploads/2019/01/037_BPR_e1.pdf. [cited 2019 August 26].
[42] Ferner RE. Post-mortem clinical pharmacology. Br J Clin Pharmacol. 2008;66(4):430-43.
[43] Pleuvry BJ. Pharmacodynamic and pharmacokinetic drug interactions. Anaesthesia & Intensive Care Medicine. 2005;6(4):129-33.
[44] 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;47(11):1980-4.
[45] Jones AW, Holmgren A. Concentration ratios of free-morphine to free-codeine in femoral blood in heroin-related poisoning deaths. Leg Med (Tokyo). 2011;13(4):171-3.
[46] Ellis A, McGwin G Jr, Davis GG, Dye DW. Identifying cases of heroin toxicity where 6-acetylmorphine (6-AM) is not detected by toxicological analyses. Forensic Sci Med Pathol 2016;12(3):243-7.
[47] Madras BK, Kaufman MJ. Cocaine accumulates in dopamine-rich regions of primate brain after i.v. administration: comparison with mazindol distribution. Synapse. 1994;18(3):261-75.
[48] Cone EJ, Fant RV, Rohay JM, Caplan YH, Ballina M, Reder RF, Haddox JD. Oxycodone involvement in drug abuse deaths. II: Evidence for toxic multiple drug-drug interactions. J Analytical Toxicol. 2004;28(7):616-24.
[49] 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. Available from: http://www.cdc.gov/nchs/data/misc/hb_me.pdf. [cited 2019 August 26]
[50] Gill JR. The syndrome of excited delirium. Forensic Sci Med Pathol 2014;10(2):223-8. doi: 10.1007/s12024-014-9530-2.
[51] Ehret GB, Voide C, Gex-Fabry M, Chabert J, Shah D, Broers B, Piguet V, Musset T, Gaspoz J-M, Perrier A. Drug-induced long QT syndrome in injection drug users receiving methadone: high frequency in hospitalized patients and risk factors. Arch Intern Med. 2006;166(12):1280–7.

[52] National Center for Health Statistics. Vital Statistics Reporting Guidance, Report No. 2. A reference guide for completing the death certificate for drug toxicity deaths, 2019 May. Available from https://www.cdc.gov/nchs/data/nvss/vsrg/vsrg02-508.pdf. [cited 2019 August 26].

[53] Rosenberg ML, Davidson LE, Smith JC, Berman AL, Buzbee H, Gantner G, et al. Operational criteria for the determination of suicide. J Forensic Sci. 1988;33(6):1445-56.