Interpretation and Death Certificate

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Learning Objectives

• Become familiar with the OSAC/NAME recommendations and guidelines
• Know how to report the toxicology results and autopsy findings
• Know the case definitions for drug-caused death, drug poisoning death, drug-detected death, and drug
Medicolegal Death Investigation Subcommittee Recommendations

• 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

• A complete scene investigation extends to reconciliation of prescription information and pill counts

• Blood, urine, and vitreous humor when available, should be retained in all cases

• A toxicological panel should be comprehensive and include opioid and benzodiazepines, as well as other potent depressant, stimulant, and anti-depressant medications

• Interpretation of postmortem opioid concentrations requires correlation with medical history, scene investigation, and autopsy findings

• If death is attributed to any drug or combination of drugs, the certifier should list all the responsible substances by generic name in the autopsy report and on the death certificate
Toxicology Interpretation

• Data interpretation of toxicology report must be taken with careful and critical consideration of other information
False Assumptions for Toxicology Interpretation

- Postmortem blood drug concentrations reflect those at the moment of death
- Blood drug concentrations are reasonably predictable
- Pharmacokinetics is useful in postmortem cases
- Drug dose can be estimated from postmortem blood concentrations
Possible Interpretations Problems

- Sample Integrity
- Postmortem Neo-formation
- Postmortem Redistribution
- Site-to-site differences
- Postmortem Diffusion
- Trauma Artifacts
- Medical Artifacts
- Delayed Deaths
- Drug Instability (metabolism)

- Drug-drug/alcohol interactions
- Impaired Metabolism (& PG)
- Impaired Clearance
- Iatrogenic Deaths
- Tolerance/Opiate Deaths
- Improper Use of Literature
- Improper Use of Pharmacokinetics
- Unwarranted Confidence
Postmortem Fermentation

- Blood on its own is unreliable as a specimen for assessing the presence of alcohol at the time of death
- Ethanol in specimen ingested or produced?
- Contaminated samples due to excessive trauma, decomposition, bacterial infection
- Use Blood and Vitreous
- Postmortem BAC can get up to legal limit due to fermentation
  - Rare circumstances $>300$ mg/dl or 0.300 BAC.
Interpretation

- Drug level: therapeutic, toxic or fatal?
- Compare measured blood concentrations with concentrations reported in the literature
  - Reference materials
  - Clinical pharmacology studies
  - Incidental drug findings
  - Plasma or serum is not blood
- Case History
  - Symptoms observed by witnesses
  - Individual tolerance to the drug
Other Interpretation Issues

• Combined Drug Deaths
  • Additive or synergistic toxicity

• Tolerance
  • Need to increase dose for same effect

• Genetically Impaired Metabolism
  • 7-10% Caucasians are slow metabolizers

• Drug-Drug Interactions
  • Can cause synergistic or fatal toxicity
Other Interpretation Issues

• Drug Accumulation
  • Caused by decreased metabolism or clearance

• Medical Artifacts
  • Intravenous lines
  • Incomplete distribution

• Delayed deaths
  • Drug toxicity causes physiological damage
  • Drug levels may fall to near zero before death occurs
Medical Artifacts

• Intravenous lines/drug pumps
  • May continue to run after death – local buildup

• Medications injected near death
  • Incomplete distribution of lidocaine
  • Terminal dosages of narcotics

• Organ harvest drugs
  • Papaverine for saphenous vein
Delayed Deaths

• Depressants (narcotics, sedatives) with or without alcohol can cause hypoxic brain damage

• Resuscitation and hospitalization for hours or days can lead to Low or near absent levels
  • Even without resuscitation, drugs can lead to prolonged coma prior to death, and low drug levels
  • Near-fatal ethanol can clear in <24h

• Delayed deaths also a factor with acetaminophen, ethylene glycol and methanol

• Antemortem and hospital admission specimens important
Tables of therapeutic ranges

Temptation to interpret from tables of so-called normal concentrations

- Nice neat ranges
- Often based on clinical studies or single cases
- Ranges
  - Often do not allow for postmortem change
  - Do not state whether death was delayed
  - Do not state whether other drugs or alcohol present
  - Allow for individual circumstances
    - Example: fentanyl 1 – 2 ug/l or 50 – 100 ug/l
- Advise against using them or relying heavily on them
Importance of History: Tolerance

- State of decreased responsiveness due to long term exposure
- Drug concentrations in non-drug related deaths may overlap with reported drug concentrations in fatal drug intoxications
- Methadone example:
  - Deaths due to methadone are associated with blood levels > 2 mg/mL
  - Patients on methadone maintenance – peak blood concentrations may range up to 9 mg/mL
Acute vs. Chronic Ingestion

- Parent:metabolite drug concentration ratio may be of assistance in differentiating between acute and chronic ingestion of a drug
- Parent >> Metabolite
  - Suggestive of acute overdose and rapid death
- Parent < Metabolite
  - Slow death and/or chronic administration
Metabolites

- Metabolites are produced when drugs are biotransformed (converted) into other chemicals by enzymes
- Metabolite drug concentrations may be the more useful measure of exposure or toxicity
- The purpose of metabolism is to detoxify substances to make them more easily excreted from the body
Metabolites: Exposure

• The parent compound may be a prodrug or may have a shorter $t_{1/2}$ than the metabolite, so metabolite is detected by analysis

• Prodrug is an inactive substance that has an active metabolite

• Clorazepate, nordiazepam

• Flurazepam, N-desalkylflurazepam

• Heroin, 6-Acetylmorphine, morphine
Metabolites: Toxicity

- The metabolite may have more toxicity over the parent compound:
  - Acetaminophen, N-Acetylbenzoquinoneimine
  - Meperidine, normeperidine
  - Methanol, formaldehyde, formic acid leads to blindness by destruction of the retina and optic nerve degeneration
  - Ethylene glycol, oxalic acid, calcium oxalate leads to crystals
Case of Fatal Drug Accumulation

- 21 year old student living with parents
- History of well controlled manic depression
- Watching TV with father, but feeling unwell and went to bed early
- 2 h later complained of nausea
- 4 h later was heard to collapse and taken to hospital
- died en route, resuscitation failed
- All medication accounted, no sign of overdose
- Prescribed: chlorpromazine, imipramine, amphetamine
- No cause of death at autopsy
Fatal Drug Accumulation
Toxicology Results

<table>
<thead>
<tr>
<th></th>
<th>Chlorpromazine</th>
<th>Imipramine</th>
<th>Desipramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral blood</td>
<td>0.92</td>
<td>0.60</td>
<td>3.74</td>
</tr>
<tr>
<td>Liver</td>
<td>111</td>
<td>37</td>
<td>261</td>
</tr>
<tr>
<td>Stomach</td>
<td>trace</td>
<td>trace</td>
<td>trace</td>
</tr>
</tbody>
</table>

Results: mg/l or mg/kg

- Liver levels VERY high, especially metabolite desipramine
- Very high desipramine (metabolite) to imipramine suggests accumulation
- Likely genetic (P4502D6) and/or drug-drug induced accumulation
- All medications accounted for (none missing)
Impaired Metabolism

• Genetic impairment due to enzyme deficiency
  • Cytochrome P<sub>450</sub>2D6 in 7-10% Caucasians
• Drug-Drug impairment of enzyme system
  • Impairment by SSRIs of CYP<sub>450</sub>2D6
• Impairment due to high single drug concentration
• Impairment due to reduced liver function (age, alcohol), kidney function
Iatrogenic Deaths

Unintended deaths due to adverse effects of medically prescribed drugs

- Adverse reactions such as anaphylaxis
- Hematological, hepatic or renal adverse effects
- Serotonin syndrome and Neuromuscular Malignant Syndrome (NMS)
- Inadvertent overdose (narcotics)?
- First three may not be dose-related
Tolerance / Opiate Deaths

• Interpretation of postmortem narcotic blood levels
• Need to have some idea of degree of tolerance
  • If naive user, interpretation easier
  • If prescribed, need medical record and/or pharmacy record
  • Need to know dose and duration of dosage
  • Need medication count
Improper Use of Pharmacokinetics

Amount (dose) = C x Wt x Vd

- C = plasma concentration of drug
- Wt = body weight
- Vd = volume of distribution

Unknown

- Volume of distribution for that person
- Blood drug concentration at time of death
- Whether drug concentration was at “steady state”
How to Interpret

• Interpret with full consideration of:
  • Circumstances of death
  • Post-death investigation including:
    • Medical history
    • Medication history
    • Autopsy findings
    • Toxicology on alternate specimens

• Don’t provide an interpretation if there is not enough information
Medication Counts

Rationalize for each important medication

- Number prescribed
- Date dispensed
- Dosage (e.g. tablets per day)
- Number remaining at death
- Calculate meds “unaccounted for”
- Suicide vs. “Build-up”…
Complete Investigation

- A complete medicolegal death investigation is crucial
- The more information, the more accurate the whole picture
- Sometimes you have to look for information
  - Circumstances, scene, witness accounts
  - Past medical and medication history
  - Autopsy findings
- Recognize that sometimes you just don’t have enough information
Thinking Points

• Many drug users have been ingesting the substances for considerable periods of time.
• Why did it kill today?
• Without an autopsy to identify comorbidities and their relative risk, we are guessing.
• For some cases, an apparent drug death may have no comorbidities and negative toxicology.
• Is that a case where a new substance that is not part of the usual panel detected by the laboratory or is it below the threshold of detection?
• New synthetic opioids can kill at very low doses, close to or below the threshold of detection.
Toxicology Findings

• Prescribed medications
• Summary of testing
  • Consistent positive findings
  • Inconsistent positive findings
  • Inconsistent negative findings
• All findings
  • Opiates, benzodiazepines, anti-depressants, sleep aids, etc.
• Explanation of consistent positive results, inconsistent positive results, and inconsistent negative results
• Specimen validity
• Specimen location and tissue (“blood from femoral vein”)
Determination of COD and MOD

- Accurate determination of cause and manner of death must include consideration of scene investigative findings, the decedent’s medical and drug use history, autopsy findings, and toxicological testing.
- The cause of death statement, both on the autopsy report and death certificate, should include the list of generic names of drugs to have caused or contributed to death.
- No vague descriptions
  - Polypharmacy
  - Drug abuse
  - Mixed drug intoxication
Death Certificate Data

• Death certificates are the sole source of mortality data
• Death investigation and reporting inconsistencies
  • Incomplete and inconsistent Cause of Death
• On 25% of death certificates do not specify drug in cause of death
Overdoses Manner of Death

- Deaths from the misuse or abuse of drugs without apparent intent of self-harm are best classified as accident
- Deaths from the misuse or abuse of drugs with apparent intent of self-harm as suicide
- Reserve undetermined manner for use in cases in which evidence may support more than one possible determination
- Rare cases of homicide with direct administration of drug to another individual that causes death
Case Definitions

Drug-Caused Death

• A death that has been certified as resulting from exposure to a drug, either alone or in combination with other drugs or substances
• Intent is irrelevant
• Evidence of drug will be found on post-mortem toxicology; rare instance when toxicological testing is not available or was omitted by circumstantial evidence is sufficient
• Includes: acute drug toxicity, chronic drug effects, adverse drug reactions/effects, legal executions by drugs, terrorist events involving drugs, and mental and behavioral disorders to drugs
• Excludes: Deaths from infections resulting from drug use such as IV drug use and deaths from congenital anomalies resulting from drug use
Case Definitions

Drug-Poisoning Death (a proposed subcategory of drug-caused death)

- Equivalent to the layperson’s concept of a drug overdose
- Death due to acute exposure to a drug, either alone or in combination with other drugs or other substances
- Intent is irrelevant
- Evidence of drug will be found on post-mortem toxicology; rare instance when toxicological testing is not available or was omitted by circumstantial evidence is sufficient
- Includes: acute toxicity from drugs used recreationally, drugs given or taken in error, drugs taken that were prescribed to another person, and overdose in a medical setting
- Excludes: Deaths from infections resulting from drug use such as IV drug use and deaths from congenital anomalies resulting from drug use, chronic drug effects, correct drug properly administered in a therapeutic or prophylactic dosage as the cause of any adverse effect, legal executions, terrorist events involving drugs, and mental and behavior disorders due to drugs
Case Definitions

Drug-Detected Death

- A death in which a drug is detected in postmortem testing, regardless of the drug’s role in causing the death
- Intent is irrelevant
- Evidence of the drug must be found on postmortem analysis; rare instance when toxicological testing is not available or was omitted by circumstantial evidence is sufficient
- Includes: All deaths, whether natural or a result of trauma (e.g. motor vehicle crash and suffocation), in which a drug is detected, and all drug-caused and drug poisoning deaths
- Excludes: Deaths for which the toxicology was performed postmortem by staff of a hospital or other medical facility
Case Definitions

Drug

• Any chemical compound that may be used by or administered to humans or animals as an aid in the diagnosis, treatment, or prevention of disease or injury for the relief of pain or suffering; to control or improve any physiologic or pathologic condition; or for the feeling it causes

• Includes: Illicit drugs such as heroin, cocaine, and hallucinogens; prescription drugs; over-the-counter agents; biological substances such as vaccinations, veterinary drugs, dietary supplements; and nonmedical substances such as inhaled solvents

• Excludes: Alcohol and tobacco and the toxic effects of other noxious substances eaten as food, such as hallucinogenic mushrooms
Documenting Causality on the Death Certificate

• All drugs that are deemed physiologically significant in causing death should be listed individually in Part 1 of the cause of death portion of the death certificate

• Part II is reserved for preexisting or coexisting conditions that contributed to death but are not the underlying cause of death listed in Part I
  • The intention is not to put the most lethal drugs in Part I and the less lethal drugs in Part II, but for the role the drugs played in contributing to the death to be the factor that determines whether a drug should be reported in Part I or II.

• Drugs that did not contribute to the cause of death should not be recorded on the death certificate
Documenting Causality on the Death Certificate

• Specifying individual drug names on the death certificate is important because death certificates are the source documents for national mortality statistics
• In general, it is better to record the parent drug than the drug metabolite
• When reporting a death due to the acute toxic effects of a drug, use toxicity, toxic effects, intoxication, or poisoning in the Cause of Death portion of the death certificate
• Avoid the words use or abuse, which – along with terms such as dependence and disorder – would be appropriate to use only if the intent is to implicate substance use as the cause of death
• Addiction and disorder are appropriately used to describe long-term drug dependence or drug addiction that has caused physiological damage to a point at which a natural death occurred (as through organ failure)
• Avoid overdose because it lacks specific meaning
Manner of Death Interpretation

• Most classified as accident
  • Unintentional injury
  • Default for drug death
• Some undetermined
• Underreported suicides
  • No clear intent
  • Unwitnessed
  • Prior history of repeated drug abuse leans towards the accident
  • Regional beliefs
• Homicides also can occur
  • Unwitnessed
  • No clear evidence
Accidental Drug Death Reclassification

- Death can arise from deliberate and motivated behaviors that can increase probability of death
- Drug abuse could be classified as self-harm
- Proposed use of Death from drug self intoxication (DDSI)
Case 1
Multiple Drug Use in a Tolerant Individual

• A 40-year-old man with a history of substance use disorder engages in drug use with friends and goes to sleep.

• The next day, he could not be awakened. Emergency medical services are summoned, and he is found dead.

• At autopsy, he is found to have pulmonary congestion and edema, with a bladder full of urine. No indication of a specific disease or injury that caused his death.

• Toxicologic Analysis reveals low-toxic concentrations of oxycodone and diazepam
Case 1
Multiple Drug Use in a Tolerant Individual

• Cause of Death, Part I: Acute intoxication by oxycodone and diazepam
• Cause of Death, Part II: None
• How Injury Occurred: Ingested diazepam and injected oxycodone intravenously
• Drug-caused death: Yes
• Drug poisoning death: Yes
• Drug-detected death: Yes
• Comment: Because of tolerance, high blood concentration of opioid or ethanol would be expected to produce the ultimately fatal toxicity. During the coma, he would have metabolized a significant amount of the drug, thus lowering postmortem concentrations.
Case 2

Single Drug Use in a Non-Tolerant Individual

• A 45-year-old woman found dead in bed.

• She has no history of a substance use disorder but has been treated for years with various opioid analgesics for fibromyalgia. Her physician prescribed methadone 4 days earlier.

• Toxicology reveals a methadone concentration that would be toxic to a non-tolerant individual, but no other evidence of injury or disease.
Case 2
Single Drug Use in a Non-Tolerant Individual

• Cause of Death, Part I: Acute intoxication by methadone
• Cause of Death, Part II: History of chronic pain
• How injury occurred: Ingested methadone
• Drug-caused death: Yes
• Drug poisoning death: Yes
• Drug-detected death: Yes
• Comment: Death was solely due to drug intoxication in an individual who was not tolerant to the drug’s effects
Case 3  
Homicide with a History of Drug Use

• Police are called to a known drug-dealing location because of the sound of gunshots. When they arrive, they find a 22-year-old man with multiple gunshot wounds to the head.

• He is pronounced dead at the scene. Multiple witnesses confirm that the decedent was selling cocaine at the time he was shot.

• Autopsy reveals two contact entrance gunshot wounds to the back of the head, with perforations of the brain and exit wounds of the forehead.

• Toxicologic analysis reveals a lethal concentration of a drug
Case 3
Homicide with a History of Drug Use

• Cause of death, Part I: Gunshot wounds to the head
• Cause of death, Part II: None
• How injury occurred: Shot with [type of weapon] by other(s) while selling cocaine
• Drug-caused death: No
• Drug poisoning death: No
• Drug-detected death: Yes
• Comment: The presence of the drug may be significant circumstantially in explaining why the individual was in the situation where he was shot. This demonstrates the importance of identifying drug-detected deaths, even though the drug did not itself cause or contribute pathophysiologically to the death.
Case 4
Drug Poisoning with Contributing Medical Condition

- A 52-year-old man with a history of high blood pressure smoke crack cocaine. Shortly after doing so, he complained of severe headache, collapsed, and died.
- Toxicology indicated acute cocaine intoxication and presence of alcohol and alprazolam.
- Autopsy indicated hemorrhage in the brain in a location typical of hypertensive hemorrhages.
Case 4
Drug Poisoning with a Contributing Medical Condition

- Cause of death, Part I: (Line A) Intracerebral hemorrhage; (Line B) Due to acute cocaine toxicity
- Cause of death, Part II (other significant conditions): Hypertension
- How injury occurred: Smoked crack cocaine, thereby exacerbating underlying hypertension
- Drug-caused death: Yes
- Drug poisoning death: Yes
- Drug-detected death: Yes
- Comment: Typically, even if underlying natural disease is significant, if acute intoxication exacerbates that disease and causes about natural death, preference is given to the non-natural manner of death. Thus, hypertension is mentioned in Part II.
- Note that multiple drugs were found on toxicology, but only cocaine toxicity is listed as a cause of death. The alprazolam likely did not contribute to the death
Complete Death Certification

• List specific drugs on death certificate, otherwise statistics could be underestimated
• Lack of drug specificity can limit access to data that can inform prevention and interventions efforts
  • Can limit access to funding for medicolegal death investigation systems and processes
• Proposed uniform standards and case definitions for classifying opioid related deaths
• Educate on how drug specificity assists public health efforts
  • Death certificate provide valuable data for the prevention, education, intervention and surveillance
Accurate Death Certification

• Serves public’s health and safety
• Processes served
  • Emerging threats to public health
  • Criminal and Civil Judicial processes
  • Genetic Counseling
  • Estate Resolution
  • Insurance Claims
Medicolegal Death Investigation Subcommittee Recommendations

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- A complete scene investigation extends to reconciliation of prescription information and pill counts.
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- A toxicological panel should be comprehensive and include opioid and benzodiazepines, as well as other potent depressant, stimulant, and anti-depressant medications.
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References

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