NAME FORENSIC PATHOLOGY GRAND ROUNDS 2022

VOLUME 1:
TOXICOLOGICAL CAUSES OF DEATH

EDITORS
J. KEITH PINCKARD, MD, PhD
M.J. MENENDEZ

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PREFACE

This collection of forensic toxicology-pathology proceedings is from a series of Grand Rounds presentations on drug/toxin-related deaths given from January through June 2022. The goal of the project was to encourage best practices in the accurate recording of the contribution of drugs and other toxins to death in the United States. The series featured twelve sessions from experienced practitioners in forensic pathology and toxicology who shared their knowledge and insights into the appropriate certification of these challenging deaths.

The Center for Forensic Science Research and Education (CFSRE) and the National Association of Medical Examiners (NAME), with financial support from the National Network of Public Health Institutes (NNPHI) through a cooperative agreement with the Centers for Disease Control and Prevention (CDC), offered this twelve-week series of Grand Rounds presentations. The presentations highlighted the certification of both commonplace and complex deaths involving drugs and other toxic agents. The talks reached the audience capacity of 600 attendees.

The virtual Grand Round sessions were focused on a variety of interrelated topics related to these deaths including: public health and safety, toxicological updates, autopsy and scene findings, laboratory testing, and research related to improving death investigations and drug use surveillance through monitoring

of morbidity and mortality data. The sessions used case presentations to pose questions and hypotheticals with subsequent analysis relating to the fact scenarios. The cases were viewed through the lens of the investigation, autopsy, and toxicology results, with discussion of the interpretation of toxicological factors and their incorporation into cause and manner of death determinations.

Presentations have been compiled into this eBook, which includes didactic materials, case scenarios, and references to the relevant academic and scientific literature from each of the twelve Grand Rounds presentations. This e-book is a compendium of resources on medicolegal death investigation; forensic pathology triaging, autopsy, and toxicology; and collaboration between public health systems to achieve best practices in vital death certificate reporting.

Funding for this training was made possible by a cooperative agreement between the National Network of Public Health Institutes (NNPHI) and the Centers for Disease Control and Prevention [6 NU38OT000303-03-02]. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Centers for Disease Control and Prevention or NNPHI, nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

This project could not have been accomplished without the dedicated work of all the speakers and the organizers who included Dr. Barry Logan, Dr. Mary Ann Sens, Dr. Laura Labay, Carrie Barron, and Josh Vickers. Special thanks are extended to the Grand Rounds moderator, Dr. Reade Quinton, and the Grand Rounds compendium editors, Dr. Keith Pinckard and M.J. Menendez. Thank you all.

James R. Gill MD

The Collision of the COVID-19 Pandemic with the Opioid Epidemic

GREGORY G. DAVIS, MD, MSPH

INTRODUCTION:

Overdose deaths, particularly from opioids, have been increasing in the United States since 2000. In 2019, overdose deaths surpassed deaths related to motor vehicles as the most common cause of accidental deaths in the United States. In late 2019, SARS-CoV-2 entered humans, becoming the worldwide COVID-19 pandemic in 2020.

Some nations have a high opioid overdose death rate and other nations have a high COVID-19 infection rate, but the United States has been the only industrialized nation to consistently be ranked at the highest level for both its COVID-19 infection rate and its opioid overdose death rate. COVID-19 has altered life, displacing individuals from normal work and social interactions and increasing isolation. The social isolation and displacement caused by COVID-19 are associated with an accelerated increase in deaths from opioid toxicity.

MAIN TEACHING POINTS:

1. The disruption of life and isolation caused by the COVID-19 pandemic are associated with an accelerated increase in overdose deaths in the United States.

2. Reversal of the overdose epidemic requires changing conditions in society that foster illicit drug use, from changes in public health policy to changes at the level of individual interactions.
3. All pandemics and epidemics eventually end.

History of Pandemics and Epidemics: History and literature record many outbreaks of infectious diseases that decimated communities, cities, or even entire countries. The worst pandemic known is the bubonic plague, the Black Death of the 14th Century. This pandemic claimed the lives of 33% of persons then living. The Spanish Flu of 1918-1920 killed 3% of the world's population. The HIV/AIDS pandemic began in 1981 and continues, killing an estimated 0.5% of the world's population.

At the end of January 2022, COVID-19 has caused over 5 million deaths, or 0.06% of the world's population. Records exist of epidemics of cholera, yellow fever, and smallpox. We have memorable historical accounts of some epidemics and pandemics – Thucydides' account of the plague of Athens and Boccaccio's account of the Black Death in Italy. Later works describe the abrupt onset of an epidemic and the horror of seeing the manifestations of disease. Poe's *Masque of the Red Death* and Frances Hodgson Burnett's *The Secret Garden* both describe the effect of cholera on those that witness the sudden onset. In time, however, all pandemics have ended.

History of Intoxication: Humans have long used intoxicating substances, primarily alcohol, but also tobacco, betel nuts, khat, or coca leaves mixed with lime juice. Alcohol is the most easily available of these substances. Alcohol forms naturally whenever something that contains carbohydrates ferments, and liquids that can undergo fermentation exist wherever there are grapes or grain to form mash.

The Bible presents both the enjoyable and the destructive natures of alcohol in Psalms ("Wine that gladdens the heart of man," Psalms 104:15) and in Proverbs ("Wine is a mocker, strong drink a brawler." Proverbs 20:1) Literary accounts typically focus on the comedy or tragedy that comes from being drunk, but the question that confronts anyone using a substance to alter their mood is where to draw the line between enjoyable and destructive.

Homer describes how Odysseus gave the cyclops Polyphemus the gift of wine. Polyphemus enjoyed this new beverage so much that he promised to eat Odysseus last as a reward, but later Polyphemus is drunk and begins

vomiting after he passes out. His stupor allows Odysseus and his remaining men to blind the giant. That detail of going from merry to drunk and then unconscious and vomiting is an account that forensic pathologists hear regularly.

Geoffrey Chaucer was born into a family of wine merchants and importers. Chaucer speaks of drunkenness in several places in his *Canterbury Tales,* but of particular interest to forensic pathologists are Chaucer's accounts of the drunken miller in *The Reeve's Tale* and of the drunken cook in the Prologue to the *Manciple's Tale*. Both are described as pale and breathing heavily, "snuffling" or "wheezing" as though with asthma or snorting like a horse. Chaucer is describing the increasingly infrequent respiratory pattern of deep intoxication, where a person goes overlong without breathing and then suddenly inhales loudly when accumulated carbon dioxide finally triggers a breath. Every forensic pathologist is thoroughly familiar with the description of a person who has passed out and is "snoring loudly" before later being found unresponsive. This heavy snoring respiration has various causes, but one cause is a deep coma caused by profound intoxication by a central nervous system depressant. Alcohol is a central nervous system depressant, but one must reach a blood ethanol concentration of around 0.40 g/dL (or 400 mg/dL) to die from ethanol toxicity. These days, individuals are much more likely to die from respiratory depression from opioid toxicity, whether by heroin, fentanyl, or some other opioid.

History of Current Opioid Epidemic: Figure 1 shows a graph prepared by the National Center for Health Statistics. This graph shows the beginning and development of the current opioid epidemic in the United States. In 1995, the American Pain Society began a campaign to encourage physicians to assess and treat pain with pain relief medications, particularly opioid preparations. By 2000, various agencies, such as the Joint Commission, American Medical Association, American Academy of Family Physicians, and the Veterans Administration had endorsed this campaign to make treating pain a primary goal of medical care. **Figure 1** shows that deaths from prescription opioids rose steadily during the decade from 2000 to 2010.

By 2011, the number of overdose deaths from medical opioids had quadrupled in the course of a decade, and agencies that had endorsed the campaign to relieve pain had rescinded their endorsement. In 2013, physician prescriptions for medical opioids fell for the first time since 2000. As it became more difficult to acquire prescription opioids, individuals now physically addicted

to opioids began buying heroin. By 2015, heroin had nearly caught up with prescription opioids as a cause of death, and illicit fentanyl was beginning its ascent. Cocaine and methamphetamine were also causing more deaths than they had in the previous decade. By 2016, illicit fentanyl surpassed all other drugs in causing overdose deaths in America, and this remains true today.

Comparison of Heroin and Fentanyl: Heroin is synthesized from morphine, and morphine comes from opium poppies. Opium poppies grow in dry, warm climates, particularly in a narrow, 4,500-mile stretch of mountains extending across central Asia from Turkey through Pakistan and Burma. Shipping opium or heroin has a cost, and this cost increases price. Hence, drug cartels have begun cultivating opium poppies in Columbia and Mexico, as reported by the U.S. Drug Enforcement Agency.

Morphine is more complicated chemically than is fentanyl. Poppies naturally produce morphine, but plants take time to grow, are subject to disease and pests, and can by spotted by overhead surveillance. Fentanyl is a much simpler molecule than morphine and can be synthesized easily in a laboratory. Moreover, fentanyl is more powerful than heroin. The cost of producing a gram of fentanyl is one-tenth the cost of a gram of heroin. The potency of fentanyl allows one to multiply the margin of profit yet again, by selling smaller doses. Another advantage of fentanyl to drug cartels is that more powerful opioids are more attractive to opioid users.

Collision of COVID-19 Pandemic with Opioid Epidemic: As **Figure 1** (page 8) shows, overdose deaths in 2019 were rising for all drugs except heroin. **Figure 1** ends with data for 2019, and national data are not yet available for 2020 and 2021. To see the relationship of the COVID-19 pandemic with the opioid epidemic, one must look at local data until the national data become available. **Figure 2** (page 8) shows the overdose death data for the United States, Alabama, and Jefferson County, Alabama. Overdose deaths in Jefferson County, Alabama rose by 28% in 2020 compared to 2019 and by another 25% in 2021 compared to 2020. Similar reports have come from other jurisdictions around the United States. The overdose death rate is higher than it has ever been in Jefferson County, Alabama (55 overdose deaths per 100,000 residents in 2021), but COVID-19 is even more lethal, with a death rate of 190 deaths per 100,000 residents (**Figure 3**, page 10).

CONCLUSION:

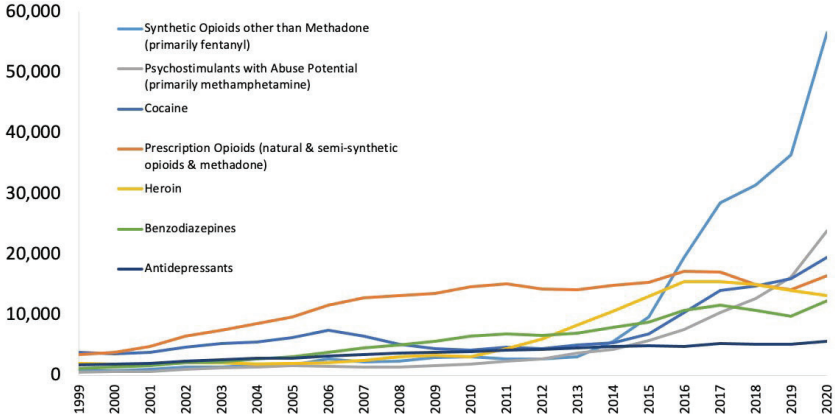
Many factors lead to death of an individual that dies from COVID-19: age, underlying medical condition, infecting dose, vaccination status, willingness to seek medical care, availability of medical care, etc. Drug deaths are also multi-factorial and we can anticipate many studies of the relationship between the COVID-19 pandemic and the opioid epidemic. Economists have performed studies that provide evidence that an economic downturn is exactly the time that a state or county should continue its drug treatment programs, not cut those programs to save money. The economic argument is that a government entity will save more money and benefit the economy in the long run by providing drug treatment programs. These studies are pertinent to the condition of American society in 2021.

Public health initiatives focus on understanding risks for illicit drug use, some of which include stressful life events, areas of poverty, and lack of opportunity. On the scale of public health governments can work to create opportunity structure to redress imbalances in opportunity. At the individual level, disability and chronic pain are associated with isolation and depression, and this becomes a feedback loop that far too often ends in death by overdose or suicide. What can we do to overcome hopelessness? It turns out that we can do much, but it demands much of each of us. The investment is not just an investment of money; it is an investment of ourselves in the lives of other individuals. The isolation that COVID-19 has forced upon us has reminded us of the importance of meaningful human interaction. At the individual level, caring to be a part of other people's lives overcomes isolation and the hopelessness that isolation breeds.

Figure 1.

National Drug-Involved Overdose Deaths*

Number Among All Ages, 1999-2020

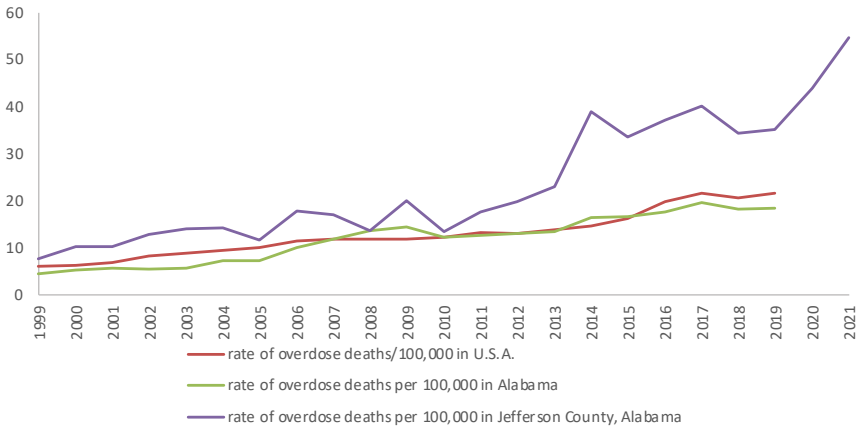


*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released 12/2021.

Available at: www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates

Figure 2.

Comparison of Overdose Death Rates



Data for U.S.A. deaths obtained from:
United States Department of Health and Human Services (US DHHS),
Centers for Disease Control and Prevention (CDC),
National Center for Health Statistics (NCHS),
Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released 2021. Data are compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program.

Data are compiled from:
2020: Multiple Cause of Death File 2020, Series 20, No. 2Z, 2021.
2019: Multiple Cause of Death File 2019, Series 20, No. 2Y, 2020.
2018: Multiple Cause of Death File 2018, Series 20, No. 2X, 2020.
2017: Multiple Cause of Death File 2017, Series 20, No. 2W, 2018.
2016: Multiple Cause of Death File 2016, Series 20, No. 2V, 2017.
2015: Multiple Cause of Death File 2015, Series 20, No. 2U, 2016.
2014: Multiple Cause of Death File 2014, Series 20, No. 2T, 2015.
2013: Multiple Cause of Death File 2013, Series 20, No. 2S, 2014.
2012: Multiple Cause of Death File 2012, Series 20, No. 2R, 2014.
2011: Multiple Cause of Death File 2011, Series 20, No. 2Q, 2014.
2010: Multiple Cause of Death File 2010, Series 20, No. 2P, 2012.
2009: Multiple Cause of Death File 2009, Series 20 No. 2O, 2012.
2008: Multiple Cause of Death File 2008, Series 20 No. 2N, 2011.
2007: Multiple Cause of Death File 2007, Series 20 No. 2M, 2010.
2005-2006: Multiple Cause of Death File 2005-2006, Series 20, No. 2L, 2009.
1999-2004: Multiple Cause of Death File 1999-2004, Series 20, No. 2J, 2007.

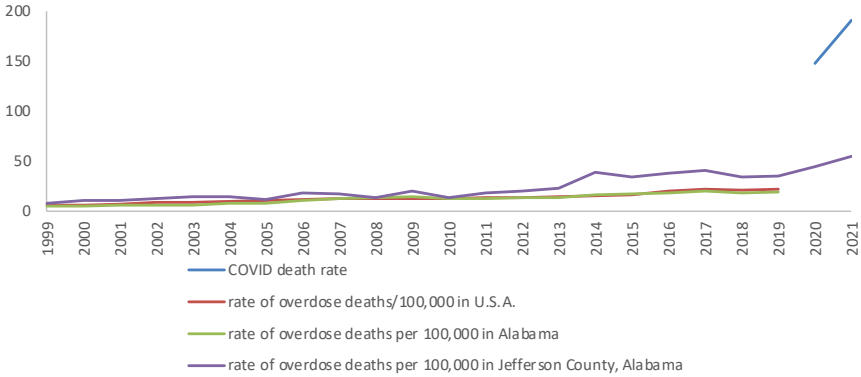
Accessed at http://wonder.cdc.gov/mcd-icd10.html. Accessed 2021 September 9.

Data for Alabama deaths obtained from https://data.cdc.gov/NCHS/NCHS-Drug-Poisoning-Mortality-by-State-United-Stat/xbxb-epbu/data, accessed 2021 September 9.

Data for Jefferson County deaths obtained from Jefferson County Coroner/Medical Examiner Office.

Figure 3.

Comparison of Overdose Death Rate with Covid-19 Death Rate



Data for U.S.A. deaths obtained from:
United States Department of Health and Human Services (US DHHS),
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2016: Multiple Cause of Death File 2016, Series 20, No. 2V, 2017.
2015: Multiple Cause of Death File 2015, Series 20, No. 2U, 2016.
2014: Multiple Cause of Death File 2014, Series 20, No. 2T, 2015.
2013: Multiple Cause of Death File 2013, Series 20, No. 2S, 2014.
2012: Multiple Cause of Death File 2012, Series 20, No. 2R, 2014.
2011: Multiple Cause of Death File 2011, Series 20, No. 2Q, 2014.
2010: Multiple Cause of Death File 2010, Series 20, No. 2P, 2012.
2009: Multiple Cause of Death File 2009, Series 20 No. 2O, 2012.
2008: Multiple Cause of Death File 2008, Series 20 No. 2N, 2011.
2007: Multiple Cause of Death File 2007, Series 20 No. 2M, 2010.

2005-2006: Multiple Cause of Death File 2005-2006, Series 20, No. 2L, 2009.
1999-2004: Multiple Cause of Death File 1999-2004, Series 20, No. 2J, 2007.

Accessed at http://wonder.cdc.gov/mcd-icd10.html. Accessed 2021 September 9.

Data for Alabama deaths obtained from https://data.cdc.gov/NCHS/NCHS-Drug-Poisoning-Mortality-by-State-United-Stat/xbxb-epbu/data, accessed 2021 September 9.

Data for Jefferson County deaths obtained from Jefferson County Coroner/Medical Examiner Office.

Data for COVID deaths in Alabama from Alabama Department of Public Health COVID-19 Data and Surveillance Dashboard, available at https://www.arcgis.com/apps/dashboards/6d2771faa9da4a2786a509d82c8cf0f7, accessed 2022 January 24.

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CHAPTER TWO

Methamphetamine-Caused and -Related Deaths

MARY ANN SENS, MD, PHD AND NIKOLAS LEMOS, PHD

INTRODUCTION:
Methamphetamine use and deaths increased dramatically in the United States since 2015, with usage and mortality continuing to climb. Methamphetamine is a central nervous system stimulant that is relatively easy to manufacture, highly addictive, and widely available which accounts for its dramatic increase in popularity and rising addiction rates.

MAIN TEACHING POINTS:

1. To appreciate the extent of methamphetamine in the communities we serve.
2. To understand the importance of methamphetamine forensic toxicology determinations in a wide variety of postmortem cases.
3. To recognize the challenges a methamphetamine finding presents in the determination of a cause and manner of death.

Basic Facts and Toxicology of Methamphetamine: Methamphetamine is a dimethyl-phenethylamine existing in two enantiomeric forms, L-(Levo) methamphetamine and R-(Dextro)methamphetamine. L-methamphetamine is found in some over-the-counter decongestants. It has low central nervous system (CNS) effects and strong peripheral sympathetic activity, which

accounts for its value as a decongestant. The mixture of the two isomers and the Dextro- or pure R-methamphetamine is a strong CNS stimulant and in contrast to the L-isomer, is a Schedule II drug.

Prescription applications include weight loss, narcolepsy, and attention deficit disorder under the trade name Desoxyn®. Methamphetamine is readily manufactured in makeshift laboratories using common cold medications as starting product. The synthesis involves some pyrogenic compounds leading to occasional fires and explosions in illicit methamphetamine laboratories.

Pharmacology and metabolism: The pharmacology of methamphetamine is straightforward, with 46-76% of the drug excreted unchanged in the urine. Methamphetamine metabolizes to amphetamine and laboratories performing analysis should look for both substances. The half-life is dependent on urine pH and ranges from 6 to 15 hours. The routes of using methamphetamine include smoking, eating, snorting, injection within a vein, and "popping" with a subcutaneous injection.

Administration of methamphetamine initially produces a "rush" of good feelings which dissipate quickly, leading individuals to repeat injections. After the rush, people using the drug report excitement and edginess often evolving to anger and fear. When using methamphetamine, individuals may have a great amount of energy, and occasionally develop severe itching and/or hyperthermia. Physiologic effects of this drug are primarily cardiovascular, with vasoconstriction and an increase in heart rate.

The effects on the CNS are significant, with mood changes as described. Chemical central nervous system (CNS) interactions from methamphetamine are not fully elucidated but may involve direct neural toxicity, an increase in dopamine concentrations, and other mechanisms within the CNS. Long-term use produces cardiovascular disease, dental problems (broken teeth, dry mouth, periodontal disease), pulmonary hypertension, generalized malnutrition, and a variety of mental illnesses including paranoia, anxiety, intense craving for drugs despite growing tolerance, visual and audio hallucinations, and delusions. All of those manifestations may persist well beyond the cessation of drug use.

Postmortem distribution: Postmortem redistribution occurs with methamphetamine and may challenge interpretation, particularly with centrally collected specimens.

Analysis and Interpretation: Methamphetamine is commonly included in a variety of screening tests for illicit substances. Cross-reactivities vary significantly among the various assays and manufacturers. It is paramount that those using and interpreting them are fully aware of their characteristics and limitations. The preferred analyses should include chromatographic/spectral confirmation/quantitation. Amphetamine is a metabolic byproduct of methamphetamine as well as a stimulant that may be illicitly produced and used but is also a prescription medication for a variety of conditions. Both methamphetamine and amphetamine should be quantified as part of the analysis and the metabolism considered in interpretation.

Interpretation: Methamphetamine concentrations may be difficult to interpret, particularly in the postmortem interval. Methamphetamine has overlapping therapeutic, toxic, and lethal concentrations. Tolerance develops when this drug is used long-term. Similar compounds, including prescribed or illicit amphetamine, may be present and complicate interpretation, making difficult the determination as to what derived from illicit D-methamphetamine. Fatal events may be precipitated by cardiovascular and neurologic stimulation in addition to direct toxicity, further adding to interpretation challenges. Hyperthermia, thought to result from aberrations in central temperature regulation, may sporadically occur, further contributing to fatalities.

Methamphetamine may pyrolyze at high temperatures, leading to interpretation challenges in hyperthermia and fire deaths by reduction of methamphetamine and alteration of the methamphetamine/amphetamine ratio. The ratio of methamphetamine to amphetamine should be close to 10:1 if the substance metabolized is D-methamphetamine. Besides a potentially legal prescription of amphetamines, many substances metabolize to methamphetamine or amphetamine in the body: amphetaminil, benzphetamine, clobenzorex, deprenyl, dimethylamphetamine, ethylamphetamine, famprofazone, fencamine, fenethylline, fenproporex, furfenorex, mefenorex, mesocarb, and prenylamine.

When the history is inconsistent with methamphetamine use or ratios suggest other drugs may be operative, a careful review of prescribed drugs particularly Benzphetamine (Didrex ®) for weight loss, Famprofazone (Gewolen®) as a nonsteroidal anti-inflammatory analgesic, and Selegiline (Atapryl®) a monoamine oxidase B (MAO-B) inhibitor in Parkinson Disease is warranted since the methamphetamine present could occur by in vivo conversion. Only the R isomer (D-methamphetamine) is illicit and unless the chiral analysis is

done, standard toxicology cannot distinguish between the two isomers. Thus, a particular case may require chiral analysis for proper interpretation.

Finally, the altered mental status and other CNS manifestations may lead to poor judgment in dangerous situations, resulting in traumatic injury as the cause of death, which may also complicate the interpretation of the role of methamphetamine.

Risks: Methamphetamine is a highly addictive CNS stimulant that is readily available and increasing in use in the United States. During 2015-2018, an estimated 1.6 million adults in the U.S. reported methamphetamine use. Of these, 53% had a methamphetamine use disorder (MUD), and 22.3% reported injecting methamphetamine. Methamphetamine use is known to co-occur with mental illness. According to the Centers for Disease Control and Prevention (CDC), overdose deaths from methamphetamine are rising, with more than 16,500 people dying in 2019. This is greater than the increase in the use of methamphetamine, indicating that the overdose risk among people who use methamphetamine is increased.

Overdose deaths from stimulants other than cocaine increased by 300% from 2015 to 2019 but the use of methamphetamine increased by only 43% during the same period and MUD increased by only 62%. Frequent methamphetamine use, defined as using for at least 100 days in the past year, increased by 66%. Overall, these data suggest a growing trend in risky use patterns, leading to an increase in overdose deaths.

Other important features of methamphetamine use are the increased diversity in user demographics and the disproportionate incidence of substance abuse disorders within different populations. Historically, middle-aged White individuals, particularly men who have sex with men, were the main users of methamphetamine. However, in recent years, methamphetamine abuse has expanded to a broader demographic. Identification as a "party" drug is replaced by a widespread, even everyday, use of this drug in a broad demographic pattern. There is a ten-fold increase in MUD without injection among Black individuals; MUD without injection also quadrupled among people aged 18-23 years, exceeding use in older populations. Deaths from methamphetamine more than quadrupled in Native American/Alaskan Natives from 2011 to 2018 (NIDA Press release, Jane 20, 2021) with sharp increases in both men and women.

Long-term use of methamphetamine is associated with decreased access to public education, stable housing, and health insurance and is positively associated with high rates of poverty, discrimination, and association with the criminal justice system. Methamphetamine use is a strong factor in health disparities. Individuals with hepatitis, HIV/AIDS, sexually transmitted diseases, or depression are at increased risk as well as those who use other substances, such as nicotine, cannabis, and cocaine. Methamphetamine use has historically been more prevalent in the Western United States but usage and availability has now become regularized in Eastern states.

Cases and Certification Issues:[1]

CASE 1:

A thirty-four year old man was found deceased in his trailer. There was blood inside the trailer, a few feet from the body. There was a history of alcohol substance abuse disorder but no illicit or inappropriate prescription drug use. Autopsy findings included a fracture of the right parietal/temporal bone, a coup/contrecoup subarachnoid hemorrhage with the countercoup injury on the left, severe hepatic steatosis with early micronodular cirrhosis, chronic obstructive lung disease, and mild cardiomegaly with biventricular dilatation.

Vitreous electrolytes:

- Sodium 117 mmol/L
- Potassium > 9.0 mmol/L
- Chloride 99 mmol/L
- Glucose < 20 mg/dL
- Urea nitrogen 27 mg/dL
- Creatinine 2.1 mg/dL

Toxicology:

- Blood EtOH: 0.070 g/dL
- Blood Methamphetamine: > 3.0 mg/L
- Blood Amphetamine: 0.29 mg/L
- Blood Phenylpropanolamine (PPA): Trace Detected
- Blood drug screen: Ethyl glucuronide, Ethyl Sulfate, Caffeine, Cotinine detected

How would you interpret findings as given and with this information?

How would you sign the death certificate?

Anatomic autopsy findings and discussion: The head injury with a skull fracture and coup/countercoup injury to the brain is a fatal injury. The particular pattern, coup/countercoup, refers to injury on one side of the brain corresponding to an impact site (coup) and a usually larger countercoup site on the opposite side. These findings indicate a moving impact, such as a fall, where the initial impact causes the brain to rebound against the opposite side (countercoup).

This pattern can occur in a fall or fall resulting from pushing but not a direct blow to a stable head. Persons with alcohol use disorder are particularly prone to falling and this injury is common in these individuals. Additionally, there was liver steatosis, early hepatic fibrosis, cardiomegaly with biventricular hypertrophy, and chronic obstructive lung disease documented at autopsy. All these conditions can lead to death; however, the head injury is more likely fatal. The liver and cardiac findings may result from long-term ethanol ingestion. The lung, and possibly cardiac, findings are usually related to tobacco use.

Electrolyte findings: The low sodium and chloride, combined with high potassium and creatinine are indicative of a prolonged interval or antemortem conditions of hyponatremic dehydration and/or chronic alcohol use disorder.

Toxicology findings: The ethanol concentration of 0.070 g/dL is just under the legal limit for driving in most states. The presence of ethyl sulfate and ethyl glucuronide are metabolites of ethanol and indicate the decedent ingested alcohol and confirms the presence of ethanol. PPA (Phenylpropanolamine) was an over-the-counter decongestant, taken off the market for humans due to side effects. Caffeine, found in many drinks and foods, is frequently present in toxicology screens. Cotinine is a metabolic product of nicotine; tobacco use is a leading cause of COPD and some cardiac diseases. A high concentration of methamphetamine is present. The value given, greater than 3.0 mg/L, indicates that the drug was at least as high as the highest standard used in the laboratory. The laboratory could, if asked, dilute the sample and get an exact number. If the sample is close to the 3.0 mg/L reported, the ratio of methamphetamine is close to the ideal 10:1 methamphetamine: amphetamine ratio.

Putting together the anatomic findings, the head injury is a fatal injury. The hepatic, lung and cardiac findings potentially are fatal but are not as definitive as the head injury. The ethanol concentration indicates antemortem drinking

of alcohol but not in quantities to produce death and the electrolyte pattern does not explain the death. Methamphetamine is potentially lethal; however, fatal drug concentrations demonstrate wide variation and this level of intoxication can be present in living patients as well as fatalities.

More definitive conclusions could be reached with testing for the actual concentrations by the laboratory. One could discuss this with the toxicologist at the laboratory; however, the head injury is definitely fatal, and is thus given as the cause of death. The remaining major findings correlate to risk factors of 1) alcohol substance abuse disorder (liver, possibly heart, ethanol concentration, and possible fall causing head injury) 2) tobacco use disorder (COPD, possible heart, cotinine), and methamphetamine intoxication. It is thus appropriate to list all major disease processes (hepatic steatosis, cardiomegaly, COPD, methamphetamine intoxication) in Part II of the death certificate: Other Significant Conditions (OSC).

Although consensus agreement was reached among polled participants regarding the head injury, a listing of the other conditions may vary with certifiers. The variation depends on training, local practice, and how convinced the signer is that these conditions contributed to the death. Some believe potentially fatal drug intoxication, if present, belongs in Part II for traumatic deaths both for public health awareness and to acknowledge the potential contribution to events leading to trauma. Others limit the death certification strictly to the cause of death. Of the viewers participating in polling during the presentation, 60% agreed with certification; 40% would not have listed methamphetamine intoxication.

Manner of death: The head injury resulted from a fall, slip or push, involving the impact of a moving head. They are common in individuals with chronic alcohol substance abuse disorder, and head injuries occasionally occur where no information is discernible as to the exact precipitating event. The manner of death would depend on whether the individual fell by himself (accident), perhaps while intoxicated, or if he was pushed or shoved by another (homicide). Since there is no information about what led to the skull fracture or coup/countercoup injury, Undetermined is appropriate for the manner. This may be amended if new information is known.

Death certification is a public health function and not a legal determination. Findings of legal culpability involve an entirely different process and is never assigned by one person. From a public health perspective, the cause of death

was a head injury; other significant (public health) conditions include heart, lung, and liver disease and acute drug intoxication.

DEATH CERTIFICATION

Part I Cause: Cerebral trauma with coup/countercoup injury

Part II Other significant conditions (OSC): Chronic obstructive lung disease, Methamphetamine intoxication, hepatic steatosis, and early cirrhosis, cardiomegaly

Manner: Undetermined

How injury occurred: Fracture of skull with coup/countercoup injury under uncertain circumstances.

CASE 2:

A thirty-four year old man was an unrestrained rear-seat passenger in a pickup truck that veered off the interstate and went down a center embankment, rolling over several times. He was partially ejected and found unresponsive. He was transported to the hospital and despite resuscitative efforts for over an hour, could not be resuscitated. He was morbidly obese; his medical history was further positive for chronic fatigue and cannabis misuse. Admission hospital laboratory values were unremarkable, with a negative alcohol screen. The drug screen was pending. The autopsy was positive for multiple extremities and rib fractures, visceral lacerations of the liver, spleen, and lungs, and cardiomegaly (650 gm).

The death certificate was signed following the autopsy with the cause of death listed as "Multiple blunt force injuries." The OSC consisted of "morbid obesity and cardiomegaly". Toxicology was drawn at autopsy but not run. When the hospital drug screen was returned, it was positive for methamphetamine and THC but had insufficient quantity to quantitate. After obtaining budget clearance to run the sample, the following results were obtained from a sample of femoral blood: Methamphetamine: 9.9 mg/L; Amphetamine: 0.46 mg/L; THC: 1 ng/mL; THC-COOH: 8 ng/ml.

Do you agree with the death certificate?

Given the new findings, how would you sign the death certificate?

Do you sign a preliminary or pending death certificates= or wait until all autopsy findings are known?

Case discussion on certification: First, should you wait to file a death certificate until all information is present? In general, death certificates are ideally filed by the funeral homes within three days of death and medical completion within seven days. Ideally, routine studies would be available in two weeks; however, with overloads of all laboratories, toxicology results may take longer.

Prompt death certification filing is needed for the closure of financial matters and estate. Social security and other payers pay states for prompt provision of death information to avoid issuing payments. There is some variation, as revealed by the audience participation when this was presented. A minority of jurisdictions issued preliminary or pending death certificates prior to knowing all autopsy findings, particularly toxicology findings. This allows some necessary financial and estate duties to initiate. A disadvantage is that many institutions, such as life insurance companies, generally require complete autopsy findings for action. Some states have "fact of death" filings, to allow notification of financial and other interests of the death as soon as death is confirmed and allow longer periods of time to complete autopsy studies.

The advantage to having all needed information in filing a death certificate is that the family gets consistent information, no incorrect copies are issued, and the case is assigned the cause and manner of death intended. If pending is listed or amendments made, erroneous copies can be in circulation, families may become suspicious and question toxicology findings added late, and sometimes families are billed each time the death certificate is issued or amended.

Cause of death discussion: Multiple blunt force injuries is an accepted cause of death, particularly when one injury is not disproportionally severe. The autopsy report should provide more detail as to the types of injury and these may be needed for trauma or other registries. Many individuals would further clarify this cause as from a single-vehicle motor accident. Some may add "unrestrained passenger" for further clarity. For public health, the fact of a motor vehicle accident or not is needed.

Some individuals will list this in Part 1; for example, Multiple blunt force injuries due to a motor vehicle accident; others will use the required field for injuries "How the injury occurred" to relate the vehicle accident. There are other fields in most death certificates relating to the motor vehicle accident and position of the decedent (driver/operator, passenger, pedestrian, bicycle, etc.).

Role of methamphetamine and interpretation of results: The methamphetamine concentration of 9.9 mg/L is high— well within the toxic range, but clearly, this individual was alive with a high concentration. The methamphetamine: amphetamine concentration is above 10:1 and precursor drugs to methamphetamine were not found on toxicology examination nor were they suspected from the history. These results could indictate very recent use of methamphetamine prior to full metabolism or postmortem redistribution of a modestly lower amount. This illustrates the wide variation in lethal methamphetamine concentrations and challenges in interpretation.

Other contributing conditions: Many individuals would not list any other contributing conditions. None of the listings are directly related to the death, although all may be valuable for public health reporting and intoxicants, in particular, are tracked in traffic accidents. In this case, the medical examiner chose to list these conditions and amend the death certificate when the methamphetamine concentration was known.

Manner of death: The manner of death in traffic fatalities, by convention, is accidental except in rare circumstances where definitive evidence exists that a car is used as a weapon (homicide) or as a means of suicide. Using that reasoning, this case is an accident. There was general agreement for this case. This would not prevent any legal action, criminal or civil. The death certificate is a document for confirming death and a public health tool for disease and death classifications. Although used for some civil legal activities such as estate and financial transfers, the death certification is totally independent of criminal legal activities and never should be substituted for the criminal justice process.

DEATH CERTIFICATION

Part I Cause: Multiple blunt force injuries (due to single motor vehicle accident, an unrestrained passenger with ejection)
Part II: Morbid obesity, cardiomegaly, methamphetamine intoxication
Manner: Accident
How Injury Occurred: Passenger in single vehicle rollover with partial ejection

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CASE 3:

A man broke down the door of a hotel room occupied by four guests. The assailant was screaming incoherently at the occupants and fired a weapon at one of the two men in the room. The nonfatally injured individual grabbed a large hunting knife and stabbed the assailant in the abdomen as he and the other guests ran from the room. Police found the assailant in a hotel corridor, profusely bleeding from the stab wound. He was transported to the nearest hospital but died within 15 minutes of arrival.

Autopsy findings: The sharp force injury to the abdomen
Entrance: superior and to the left of the umbilicus.
Injuries: perforation of the liver and inferior vena cava, ending at the vertebral column with over two liters of blood in the abdomen.
Pathway of the stab wound: front to back, left to right, and downward.

No other anatomic findings were present and no evidence of natural disease processes.

Toxicology studies on the admission blood from the hospital's emergency department revealed:
Ethanol 0.009 g/dL
Amphetamine 0.23 mg/L
Methamphetamine 2.74 mg/L

Anatomic interpretation: The location and injury of the stab wound caused massive exsanguination from severing both the liver and inferior vena cava. There is no doubt that this is the cause of death. This can be listed as the underlying cause as given "stab wound to the trunk." A more detailed cause

is also correct such as "Exsanguination due to severing of IVC due to stab wound to the trunk." In both cases, the underlying cause of death is a stab wound to the trunk, and "How injury occurred" indicates that he was stabbed by another person.

Toxicology interpretation: The concentration of methamphetamine is high and is within a potentially lethal range. The sample was taken from antemortem blood drawn on admission to the emergency department. Even with the patient essentially moribund, the short interval would generally preclude significant consideration from redistribution and could potentially be low from fluid resuscitation efforts. The ratio of amphetamine and methamphetamine is close to 10:1, indicating a normal metabolic pattern.

Correlating the decedents' behavior, the breaking down of a door to a hotel room, incoherent yelling, and assault on another, there may be signs of the stimulant and intoxicant effect of methamphetamine. From toxicology concentrations and from correlating history, this individual was intoxicated with methamphetamine. Methamphetamine has been known to produce extreme dissociative physiologic states with hyperthermia, massively increased physiologic strength, incoherent speech and behavior, paranoia, violence, and other features associated with a stimulant-induced hyperadrenergic autonomic dysfunction, sometimes termed "Excited Delirium" in the U.S. or "Acute behavioral disturbance" in the U.K. and other countries, although such occurrences are rare. This individual had some features of this disorder but several key features, such as hyperthermia, were not documented.

In this case, the certifier did not list any conditions in Part II. This illustrates the range of approaches taken in death certification. Clearly, the extent of injuries would be fatal without any methamphetamine. However, without injuries, the methamphetamine was in a lethal range and by history, the decedent exhibited signs of stimulant intoxication.

Certifying the death as it is given is more in line with instructions of death certification, restricting the death to major findings; certification with the potentially fatal concentrations of a drug in Part II is informative for more understanding of the context of the attack and public health information of drug intoxication.

DEATH CERTIFICATION

Part I Cause: Stab wound to the trunk
Part II OSC: [Not listed]
Manner: Homicide
Injury: Stabbed by another

CASE 4:

Authorities responded to a house fire at a rural location. The house was fully engulfed in flames and when extinguished, firefighters found a severely charred body inside. Most of the head and extremities were burned away and deep charring of the torso was present. The homeowner lived alone and initially, the body was assumed to be him; however, he was seen alive later in the day. Further investigation revealed a 17-year-old runaway boy had stayed at homes and barns in the area and this individual could not be found.

Autopsy findings: The body bag was radiographed in entirety prior to opening and three suspicious metallic objects were observed; two in the chest and one in debris. These were confirmed as buckshot on direct examination. Cutting into tissue along the chest wall opposite the projectiles revealed a cherry red path through the left axilla. Plastic filler, soot, and a plastic wad were also recovered. There was no generalized cherry red lividity to the body and there was minimal soot in the airway.

Investigation: When pellets were confirmed at autopsy, this was relayed to law enforcement. Independently, they had a report of the homeowner burying a shotgun and clothing on a neighbor's property after the fire. They also had a description of clothing the boy was seen wearing the days before the fire. Dental records were obtained from the boy's mother and DNA swabs from the mother and two siblings; paternal DNA samples could not be obtained.

Identification: Identification is a critical part of any forensic autopsy and death certification. In this case, the initial circumstantial identification of the homeowner was incorrect. There was a small fragment of clothing protected by the back which was consistent with the clothing described for the missing boy. The maxilla was completely missing from the conflagration, but a portion of the mandible remained with four teeth. Radiographs of the

remaining mandible confirmed third molars near the eruption, consistent with the presumed victim's age of 17 years and no discrepancy with existing dental records, but the only dental work was on teeth lost in the fire, so definitive identification could not be made. Scientific identification was made from DNA obtained from the liquid expressed from the spleen of the decedent compared to his mother and sibling.

Toxicology:

The following results were obtained from residual blood within the heart:

Carbon monoxide: 15.4%

Drug screening (LCMSTOF): Carboxy-THC glucuronide, Cotinine, Levetiracetam

Methamphetamine 1.3 mg/L (LCMSTOF)

Amphetamine 0.32 mg/L (LCMSTOF)

Interpretation and death certification: The shotgun wound was contact or near-contact for the wadding, soot, and filler particulate to enter the body. Although anatomic damage attributed to the shotgun blast was partially obliterated from the fire, the massive power of a contact/close-range shotgun blast is invariably fatal. Without skin or clothing findings, distinguishing between contact and close-range blast is impossible; however, the range must be close enough to allow entrance and embedding of soot, particular matter, and wadding within the body. The carbon monoxide concentration is elevated; in smokers, this can easily reach 10-12 %. Fatal carbon monoxide concentrations, particularly in an uninjured, otherwise healthy teen should exceed 50%.

The low concentration of carbon monoxide supports the interpretation that the shotgun blast occurred before or close to the time that the home was set on fire. Further supporting this is the anatomic finding of minimal soot in the airways. Cotinine confirms the teen was a smoker, so mildly elevated carbon monoxide should be present. The levetiracetam, an anticonvulsant medication, raises the question of epilepsy; however, there is no history of seizure disorder and no visits to any medical provider in the last four years except for dental work on a front molar. It is assumed the teen obtained the levetiracetam illicitly, perhaps thinking it was another recreational drug.

The concentration of methamphetamine present is within that reported for toxicity, however, the massive trauma present from a shotgun blast would outweigh the consideration of methamphetamine as a cause of death. The

ratio of methamphetamine to amphetamine is not ideal; it is less than the normal 10:1 ratio. This may represent a variation in postmortem distribution or pyrolytic destruction of methamphetamine from the extreme heat, producing charring and partial cremation of the individual.

In this case, the forensic pathologist certifying the death listed the methamphetamine intoxication in Part II. Many certifiers would not list this, particularly in a homicide, since it was not immediately linked to the cause of death. The pros and cons of these two approaches are previously listed and individual certifiers will make decisions based on training, exact circumstances of a particular case, and interpretation of events.

DEATH CERTIFICATION

Part I Cause: Contact to close-range shotgun wound to left lateral chest and axilla
Part II OSC: Methamphetamine intoxication
Manner: Homicide
Injury: Shot by another(s) then burned

CONCLUSION:

1. Methamphetamine use and deaths are increasing across the nation but are disproportionally affecting Native Americans and African-Americans. It coexists with poverty, discrimination, and association with the criminal justice system. Significant health consequences result from chronic methamphetamine use beyond substance use disorders, including increased cardiovascular disease, pulmonary hypertension, stillbirths, dental disease, and pulmonary hypertension. Severe mental illnesses, including paranoia, audio, and visual delusions, extreme anxiety, and others, may coexist with methamphetamine use and for years following remission. Methamphetamine abuse is a strong factor in health disparities.

2. Exercise caution with interpretation. There is an overlap between therapeutic, toxic, and lethal concentrations. Deaths may result from stimulant and vasoconstrictive effects on the cardiovascular system, the neurological effects of methamphetamine, including hyperthermia, and the direct toxic effects of methamphetamine. Methamphetamine

undergoes postmortem redistribution. Pyrolysis from elevated temperatures may also occur. Separation of dying with methamphetamine toxicity and from methamphetamine toxicity may be challenging. Interpretation must correlate scene findings, case history of signs and symptoms, drug use, and prescription drug history in interpreting methamphetamine use and intoxication with concentrations.

3. Other drugs may metabolize to methamphetamine, leading to the potential for improper interpretation of the source. Methamphetamine metabolizes to amphetamine, generally in the ratio of 10:1. If the concentrations do not approximate metabolic rate, consider abnormal re-distribution, pyrolysis, independent exposure to amphetamine, or other drugs producing amphetamine and methamphetamine. Consultation with a toxicologist may be helpful.

4. Methamphetamine occurs in two isomers. D-methamphetamine is usually illicit, and has significant CNS effects, high addiction potential, vasoconstriction, and stimulant effects on the cardiovascular system. L-methamphetamine is present in some over-the-counter decongestants and has only weak CNS effects.

5. Consultation with a toxicologist is strongly encouraged with methamphetamine deaths, particularly when there are deviations from the 10:1 expected methamphetamine/amphetamine concentrations, multiple drugs present, or findings that are not straightforward.

6. Do not use any drug quantitation from urine for interpretation, to infer dosage, effects, impairment, or intoxication. Methamphetamine and other drugs are affected by urine pH; the volume of urine varies by renal function, bladder emptying, hydration, and multiple other effects. Urine only demonstrates exposure to a compound at some past time. Urine is isolated within the bladder and does not reflect what the CNS and other vital systems are exposed to at that moment.

7. When there is a definitive cause of death, such as trauma or a catastrophic natural event like pontine hemorrhage, saddle embolus, or cardiac tamponade, differences of opinion may exist as to whether the death certificate should list toxicology findings such as ethanol or drug intoxication. Not listing these findings preserves the stated intent of the death certification process, keeping the listing to the actual cause of

death. However, the listing of significant alcohol and toxicology findings is common in traffic fatalities, may explain events or incapacitation leading to death, and contributes to a better public health understanding of drug and alcohol usage, effects, and prevalence.

ENDNOTE:

1. Polling results and answers reflect contemporaneous responses given by participants during the Grand Round lecture.

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CHAPTER THREE

An Opioid Death Despite Naloxone Therapy

DEBORAH G. JOHNSON, MD, MS

INTRODUCTION:

The presentation examines a tragic hospital death reported to the medical examiner's office as natural, for which the family initially refused an autopsy. This case serves as an ideal springboard to examine the difficulties of pain management, basic pharmacology of both narcotics and of naloxone, and how pathologist and toxicology laboratory can work together to arrive at the correct cause of death as well as prevent future deaths. Although thousands of opioid overdose deaths have been averted by the therapeutic administration of naloxone, naloxone is often found by the toxicologist in postmortem specimens, raising the question of what went wrong. Why did it not save the person?

MAIN TEACHING POINTS:

1. Recognize indicia of "natural" deaths reported to the medical examiner or coroner that should arouse suspicion that they are toxicology-related and should be brought in for further examination or autopsy
2. Understand the pharmacology of naloxone.
3. Understand the concept of equipotent or equiananalgesic dosing as applied to the prescribing of narcotics

4. Understand additional considerations for naloxone use in fentanyl/fentanyl analog deaths that may result from centrally mediated noradrenergic and cholinergic effects (wooden chest syndrome) rather than the respiratory depression of morphine-derived alkaloids.

CASE REPORT:

A 78-year-old woman with a history of severe peripheral vascular disease, status post left below-the-knee amputation and right femoral bypass in the remote past, was admitted to an outside hospital for right lower extremity ischemia. She had first noticed numbness two days previously, could not stand up on her right leg, and fell. Her medical history was significant for cigarette smoking (quit in 1991) and hypertension. Alcohol consumption was recorded in her medical records as one to two glasses of wine per day. At home she took 10 mg of hydrocodone three times a day for pain. Initial labs were normal except for anemia (Hgb 12.3 g/dL), hyponatremia (Na 127 mEq/L), and elevated AST/ALT (199/41 U/L).

At admission, she weighed 98 pounds. She was transferred to a teaching hospital in a neighboring city where it was decided she needed emergent surgery. Her last hydrocodone was given at 10 mg at 2005h. At 2245h, she was taken to the operating room where she underwent a femoral cutdown, bypass graft stenting, and endarterectomy, as well as a fasciotomy, taking four hours and not being transferred to the floor until around 0800h. She did well that day, except for postoperative pain issues, on a regimen of oxycodone and fentanyl (see detailed pain medication list below). She was given 20 mg of oxycodone PO and fentanyl 50 μg IV by the Pain Service at 0018h on hospital day 3 and became unresponsive about 0130h.

After two 0.4 mg doses of naloxone along with a normal saline bolus, she became responsive again, talking and following simple commands. At 0250h she again became unresponsive with systolic blood pressures in the 80s and another normal saline bolus was given. Another dose of naloxone was ordered but then canceled, as the patient awoke at 0340h and could at that time follow simple commands and was oriented to person and place. Labs were drawn at 0415h. At 0430h she became hypotensive and unresponsive again and was intubated. No additional naloxone was administered at this time or thereafter. The clinical team felt she had had a retroperitoneal bleed, and stated that her abdomen was distended, although an ultrasound failed to find any evidence of hemorrhage.

She started receiving the first of four units of packed red cells at 0800h. Other thoughts invoked an ischemic bowel or pneumonia resulting in sepsis to explain her sudden demise and decreased white count. Her condition deteriorated and at 0845h she went into cardiac arrest. She was revived with ACLS protocols but went into arrest again at 1010h and again at 1238h, at which point her family requested efforts stop. She was given 4 mg of morphine and at 1254, death was pronounced on the third hospital day. A hospital death certificate was filled out as "Cardiopulmonary collapse due to sepsis due to pneumonia"; manner natural.

A review of the pain medication given this patient during her hospital stay shows she received fentanyl 200 µg initially in the operating room shortly before midnight on the first hospital day followed by another 50 µg at ~0315h on the second day. Her pain medications after that were as follows on Day 2 and Day 3:

Fentanyl 50 µg IV @0831h, 1104h, 1225h, 1429h, 1908h, 0018h
Oxycodone 20 mg PO @0831h, 1235h, 1627h, 0018h
Morphine SR 15 mg PO @0840h, 1742h
Acetaminophen 650 mg PO @ 1020h, 1235h, 1627h, 2011h
Gabapentin 600 mg PO @0903h, 1627h, 2011h

Autopsy and Discussion of Findings: The husband initially objected to an autopsy, so only an external examination was performed the day after death, which found no significant ecchymosis anywhere over the right lower extremity or right lower abdomen except what would be expected from the usual surgical trauma to the area. The body was released to the funeral home with a strong recommendation to the family to reconsider a full autopsy.

After discussion with family members, one of whom happened to be a pharmacy technician, the husband agreed that an autopsy was needed and the unembalmed body was returned with the autopsy conducted on the third day after death. It found no anatomic cause of death: no pneumonia, no perforated bowel, no sepsis, and no hemorrhage apart from small amounts caused by resuscitation injuries to the rib cage and chest organs and a minimal focus (<6 mL) of subdural hematoma in the brain.

The only significant findings were related to fluid overload (massive pulmonary edema with combined lung weights of 2100 g, pleural effusions, ascites, and a postadmission weight gain of over 8 kg). Mild brain edema was present,

which can be secondary to reperfusion injury following a period of ischemia. Additionally, brain and lung edema are common findings in opioid-caused deaths. Microscopic sections showed no evidence of acute infection, but did show mild emphysematous change in the lungs and extensive intrapulmonary hemorrhage likely secondary to CPR. The heart and kidneys showed mild to moderate hypertensive changes and the liver was confirmed to have early cirrhosis, the etiology of which was most likely alcohol, given the history of daily wine consumption and no evidence microscopically of any other cause.

Toxicological analyses of all hospital specimens available found an elevated concentration of oxycodone that was in the "lethal" range[1] several hours after the last dose was given. By the time the labs were drawn, fentanyl was no longer above the limit for detection, but must be considered to have been present at the time of her initial decompensation and thus is part of her acute intoxication.

Neurontin (gabapentin) was also prescribed for this patient. This is an analog of gamma-aminobutyric acid (GABA), a naturally produced compound that is believed to stabilize electrical activity in the brain and reduce the release of glutamate, a natural nerve-exciting agent believed to be involved in transmitting pain signals in the nervous system. By reducing the release of glutamate, it is used to treat neuropathic pain resulting from damage to nerves or a disturbance in their function. When used in combination with opiates, it can reduce the amount of opiate needed for pain control, and patients on both must be closely monitored for signs of central nervous system depression. Although it was not found in toxic concentrations, its presence at any amount must be considered contributory to the toxicity.

The cause of death was ruled "Complications of acute mixed drug (oxycodone, fentanyl, gabapentin) intoxication due to recent vascular surgery to restore circulation to right leg due to peripheral vascular disease" with contributory factors of hypertension and pulmonary emphysema. The manner of death was accident.

Opioid and Naloxone Dosing: Prior to her surgery during this hospitalization, the decedent was receiving 30 mg per day of hydrocodone, a synthetic narcotic that is roughly equipotent to receiving 30 mg of morphine per day by mouth or 10 mg intravenously. Oxycodone is a stronger synthetic narcotic, with 20 mg of oxycodone being considered equipotent to 30 mg of morphine.[2,4]

Thus the decedent's baseline tolerance was for only one dose of 20 mg of oxycodone per 24 hours. Yet, in the hospital she received four times that amount in the span of 16 hours in addition to 300 μg of fentanyl following surgery for a total opioid dose within 16 hours that approximates seven times to what she normally would be tolerant to over the span of an entire day. That is not counting the two doses of slow-release morphine she received that were below the limit of detection in specimens analyzed.

While the comment is made in the medical record that the patient should have been able to tolerate the medication she received at 0018h because "she had been taking the oxycodone all day without an adverse events (sic)," this statement fails to take into account that the steady-state plasma concentration for a drug is achieved only after several half-lives have gone by, which for oxycodone takes 24 hours,[3] and one's tolerance for respiratory depression is much less in the middle of the night when one is sleeping than it is during the daytime. It is generally recognized that when calculating equianalgesic doses in the elderly, who typically have reduced metabolism for any drug, one should err on the side of caution.[4,5] Another cause for error was the misstatement in the records in more than one place that she was taking hydrocodone six times per day. A check of her actual prescription and with her family shows that she was instead only taking 10 mg of hydrocodone three times per day at home.

Naloxone, with a half-life of only 30-80 minutes, may need to be given repeatedly when it is up against a large amount of a narcotic such as oxycodone (half-life of 3-6 hours), which may cause prolonged respiratory depression.[1] "After administration of naloxone, patients must be monitored closely for re-emergence of CNS and respiratory depression so that naloxone can be readministered or a naloxone infusion started."[6] Some authorities state that up to 10-20 mg of naloxone may have to be used because of recurrent respiratory depression before one can conclude that it is of no use.[7]

The explanation for the abnormal lab values following her first and later hypoxic episodes is not entirely clear, but probably more related to issues of hemodilution and the effect of a near-death experience than to anything else. The decedent's weight at autopsy (116 lbs) was 18-24 lbs over the admission weight she was reported to have at the outside hospital (98 lbs) or at the second hospital (92 lbs). Measured weight at her last physician's appointment in August 2013 was 92 lbs.

This case illustrates the errors that can be made when dealing with opioid prescribing: not having an accurate picture of what the patient's usual opioid tolerance is; forgetting to take into account that the elderly do not metabolize opioids as rapidly;[8] and not remembering that naloxone has a short half-life compared to opioids and may need to be given multiple times until respiratory depression has been permanently averted.

The medical examiner's office needs to have a high index of suspicion that a toxicological cause of death is present when decedents are prescribed opioids, especially if they have a history of recent reversal by naloxone.

Potential Problems with Naloxone Use: Naloxone administration rarely can result in allergic reactions or precipitate a withdrawal state that may lead to physiological problems, such as pulmonary edema, or unmask the negative effects of other psychoactive drugs that are present.[9] Such unusual reactions should not preclude rapid administration of naloxone if an opioid overdose is suspected. Patients may rouse from unconsciousness to be combative and endanger their rescuers.

Special Cautions when Fentanyl or Fentanyl Analogs have been Administered: Fentanyl/fentanyl analogs present problems for naloxone reversal,[10] first because they are faster acting; second, because they are much more potent than the morphine family of narcotics and require much more naloxone to reverse respiratory depression; and third, because they may cause rigidity to rapidly develop in the diaphragm and respiratory muscles as well as the vocal cords (laryngospasm) that naloxone does not reverse, making intubation and chest compressions impossible. Even contraction of upper extremities can occur.[11] Anesthesiologists have been aware of this "wooden chest syndrome" for decades and can quickly treat it with muscle relaxants followed by intubation and administration of naloxone. The rigidity is believed to be a result of centrally mediated noradrenergic and cholinergic effects of fentanyl/fentanyl analogs, acting through the locus coeruleus in the pons.[12] The rapidity with which it develops can prevent overdose victims from surviving long enough for help to arrive. One case report has suggested that naloxone administration itself may cause wooden chest syndrome, but so far this has not been reported elsewhere.[13]

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Sample Collection Practices that Can Lead to Elevated or Lower Blood Drug Concentrations

CHARLES A. CATANESE, MD AND LAURA M. LABAY, PHD

INTRODUCTION:

The pre-analytical phase is the phase where the laboratory has no direct control over the testing process. It includes variables such as quality of sample collection, labeling of collection containers, and storage and shipping protocols.

Any pre-analytical steps must be performed with the mindset that any error cannot be remedied by the laboratory and may adversely affect the interpretation of toxicology results. In the age of accreditation and standardized protocols, postmortem laboratories have become adept at handling, preparing, and analyzing less than ideal specimens.

An important concept to remember is that a toxicology result only represents what was there at the time of testing, not what was necessarily there at the time of death. Any strategies that can be employed in the autopsy suite to mitigate pre-analytical variables should be deployed with each case. The focus of this presentation is to demonstrate best practices for sample collection for blood and vitreous fluid and juxtapose these practices with techniques that can cause alteration of drug concentrations within the collected samples.

MAIN TEACHING POINTS:

1. Document the source of the blood and sample collection technique. Make certain this information is provided to the person (e.g., toxicologist, pathologist) performing result interpretation.
2. Investigate as necessary the pedigree of hospital specimens. Tissue procurement or hospital admission samples are also subject to pre-analytical variables, but these often remain invisible unless collection practices are verified.
3. Ensure that sample collection containers are appropriately labeled with a unique case identifier (e.g., case number, patient name) and the matrix type. Make certain samples are appropriately stored before laboratory transport.

Sample Collection Considerations: We recognize that the choice of autopsy samples is case-dependent and some pre-analytical variables are outside the control of the forensic pathologist. These variables include but are not limited to the degree of trauma, decomposition, and medical interventions performed on the decedent. Even with this, however, some practices can assist in minimizing concentration changes within the collected matrices.

Due to the varied nature of the samples that can be collected during an autopsy and because this is case dependent (e.g., hair for cases where prior use/exposure to a substance is important, the muscle at the site of injection) this presentation will focus on the most collected matrices where toxicological interpretation must consider analyte concentrations.

Blood Collection from Internal Examination: The location of the blood draw and collection technique determines whether the blood is considered peripheral or central. The term peripheral generally means femoral blood or blood taken from outside the region of the trunk, to include the arms and legs. The femoral vessels are the largest in this category and are comparably easy to access. Peripheral samples are advantageous as compared to central blood, as the magnitude of postmortem redistribution is considered less in peripheral blood as compared to central blood.

Central blood samples include any sample collected from the trunk including iliac, subclavian, aortic, vena cava, and cardiac samples. Central samples demonstrate varying degrees of postmortem redistribution and must be interpreted with such consideration. Inferior vena cava samples will likely show greater postmortem redistribution than an iliac sample. This is

particularly true as decomposition advances. For example, cell lysis in organs such as the liver may cause leakage into the vessels, causing increased drug concentrations.

Femoral blood is typically taken by feeling for a crease at the anterior superior thigh, inserting a small gauge, large-bore needle, and moving the needle up and down, while moving it over slightly each time until the vessel lumen is penetrated and blood begins to fill the syringe. This process becomes more difficult as the postmortem interval increases due to dehydration and blood clot formation.

Different practices for peripheral blood collection exist. For example, the foot can be raised to allow gravity to help blood settle in the femoral region. Milking of the blood by running the hand from the ankle toward the thigh helps push the blood to the femoral region. These techniques are acceptable for collecting peripheral samples. In contrast, blocking the body to promote blood movement from the chest to the abdominal-pelvic region can lead to the mixing of central and peripheral blood. Aspirating blood with a needle while the body cavity is open to visualize the vessel is accurate for collection from a direct anatomic location.

One must take care, however, not to stick the needle through the vessel and aspirate body cavity fluid or gastric content which can artificially increase or decrease drug concentrations. Scooping the blood with a ladle from the pericardial sac after the heart is removed is sometimes used to collect what is referred to as mixed heart blood. Sample contamination can occur if the ladle is not appropriately cleaned in between cases or if a small cut is made at the posterior pericardial sac, allowing gastric contents to contaminate the blood sample. This can be sorted through, if suspected, by testing other samples, but leads to lost time, money, and inconvenience. Failure to document the exact anatomic location where samples were collected and the techniques utilized (e.g., blood versus femoral blood versus inferior vena cava blood) may lead to inaccurate result interpretation.

Blood Collection from External Examination: A blind stick is when a sample is aspirated with a needle and there is no visual as to the exact location where the tip of the needle lands. If the needle is not correctly situated, the collected sample may be contaminated with another sample type. For example, "blood" collected from the chest may contain an unknown quantity of adipose, fluid, and/or gastric content.

Depending upon the properties of the contaminant material, drug concentrations can artificially be lowered or elevated. For example, imagine the scenario where a blind stick collection is performed by inserting the needle into the upper chest area, the needle tip inadvertently pierces the esophagus, and purge fluid is mixed with blood. Analytical findings may indicate an elevated concentration of a drug that appears to be consistent with an overdose, but the blood drug concentration is therapeutic.

Practical experience shows that this is sometimes only discovered when one wants to review the autopsy report and learns that only an external examination was performed. In other cases, atypical or nonsensical results that are at odds with the case history often will necessitate testing of other samples, if available, or to at least question the process and technique used to collect the sample. It is prudent that toxicology results collected by blind stick are interpreted from a qualitative perspective; unfortunately, this may not be sufficient to determine the cause and manner of death. Note that blind sticks are not equivalent to those collections where a vessel is visualized or palpitated.

Vitreous Fluid: Many pathological states are revealed based upon abnormal clinical chemistry values. These include, for example, renal failure, dehydration, diabetic ketoacidosis, and malnutrition/starvation. Blood is a poor choice for this assessment due to the rapid breakdown of cell membranes. Because of this, chemistry abnormalities that were present at the time of death are more accurately reflected by the relatively acellular vitreous fluid analysis.

Vitreous fluid is also a prime specimen for ethanol testing since it is more resistant to microbial growth as compared to blood. It can also be used for drug testing as some analytes (e.g., 6-acetyl morphine) persist in this matrix. It is therefore important that collection is performed in a manner to prevent hemolysis and keep the specimen as pristine as possible. Aspiration of vitreous fluid via a needle with the needle bevel facing the retina can result in the aspiration of cells at the back of the eye and cell lysis. This can lead to abnormal electrolyte readings. To avoid or minimize cell aspiration and lysis, the vitreous fluid collection is best performed with the bevel end of the needle facing the lens side of the eye.

Sample Origin (Hospital and Organ Donors): Hospital samples are collected upon admission or during the treatment process. Depending on when these are collected relative to the time of death, toxicology findings

can better represent circulating drug concentrations as compared to autopsy samples. There are, however, considerations that are unique to these samples that should be remembered when interpreting analytical results. For example, most hospital testing is performed on serum or plasma samples. This means that a hospital sample may be prepared using a serum-separator tube that can absorb drugs leading to lower or nondetectable concentrations.

Furthermore, these samples are not often collected in tubes containing sodium fluoride preservative, which is used to stabilize drug concentrations. This is another pre-analytical variable to keep in mind, especially when comparing toxicology results between hospital and autopsy samples, and may provide a reason for apparently discrepant results.

Another example is derived from medical intervention requirements. Central lines are placed into large veins in the neck, chest, groin, or arm to administer fluids, medications, blood, or to quickly collect blood for diagnostic testing. In the event blood is collected from a central line, the sample may be contaminated with remnant drug(s) leading to elevated concentrations or diluted with fluid(s) leading to lower concentrations. Organ donation protocols may introduce analytes such as isopropanol into a sample. Patient care comes first, but clinical protocols should be well-understood so that these may be considered when performing result interpretation.

Chain of Custody: In forensic science, chain of custody is all-important. Uncertainty about specimen identity, including failure to assign a unique case identifier and documenting the specimen type and source, can derail the integrity of a case. The practice of tube labeling varies by jurisdiction but should be performed in a consistent manner across all cases. For example, some offices have the physician label the containers or have specimens labeled by a technician under physician supervision. One strategy is to start and complete one case at a time. If multiple external examinations and/or autopsies are concurrently being performed, the case samples during the collection and labeling process should not be placed on the same tabletop. Once samples are collected, they need to be appropriately stored to prevent in vitro concentration changes. Most often, refrigerated storage will suffice, but it is prudent to contact the laboratory if an esoteric test is needed for the case. From experience, written protocols, supervised training, and consistent practices ensure that analytical findings are truly associated with a specific case and help to mitigate any attacks concerning the reliability of the performed forensic procedures.

FURTHER READING:

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CHAPTER FIVE

Interpreting Drug Concentrations in Chronic Pain Patients Undergoing Palliative or Hospice Care

KATHERINE MALONEY, MD

INTRODUCTION:

Interpretation of medication concentrations in drug overdoses can be fraught with difficulty. There is a certain amount of nuance and experience required for the medical examiner given this task and it is made all the more difficult in chronic pain and hospice patients whose reactions to different medications are not expected to be the same as the so-called naive user. The goal of this talk is to discuss some of the common medications utilized by chronic pain and hospice patients and to discuss the process of interpreting their role in the cause of death.

MAIN TEACHING POINTS:

1. The most common medications utilized by chronic pain and hospice patients are opioids and benzodiazepines, although there are numerous other medications that have similar effects on the brain (e.g., alcohol, muscle relaxers, antihistamines, psychiatric medications, and numerous others) and thus need to be considered when interpreting medication concentrations in the blood.
2. When interpreting medication concentrations, it is important to remember that every patient is unique and thus, their personal reaction

to different medications and the interactions of those medications in their bodies will be different.

3. The most critical information in interpreting medication concentrations in chronic pain patients is the investigative information about the decedent, their medical and medication history, and the scene.

Common Medications: The most common medications utilized by chronic pain and hospice patients are opioid pain medications and benzodiazepines. Opioids act on the opioid receptor in the brain, causing a reduction in the sensation of pain, but also causing sedation and respiratory depression. Benzodiazepines act on the GABA receptor, causing a reduction in anxiety, among other effects, but also causing sedation and respiratory depression. It is the respiratory depressant effects of these classes of drugs that lead to death, and as such, any other medication with sedative and respiratory depressant effects will have an additive effect with these medications and can cause death.

Reference Guides: Useful reference guides when interpreting medications concentrations in a person's blood in general include Baselt's *Disposition of Toxic Drugs and Chemicals in Man* and *Molina's Handbook for Forensic Toxicology for Medical Examiners*, among others. The problem with these types of guides is that they generally describe expected medication and drug concentrations and potential effects of these medications in the baseline/naive user, but do not take into account the adaptations that a chronic user might have as the result of long-term use of the medication or the effect of drug combinations in the body. As such, while these references might be a useful initial starting point for drug concentration interpretation, they do not provide all of the necessary information that one might need.

Critical Information and Scene Findings: The most useful information when trying to determine whether or not a death is due to a drug overdose consists of the scene and investigative findings. What medications was the decedent prescribed? What medications were present at the scene? Did the medications appear appropriately utilized? When were the prescriptions last filled at the pharmacy, how many pills were dispensed, and how many pills remain? Does the decedent live with anyone or did they communicate with someone soon before death and what did that person observe? How was the decedent behaving and what was their usual behavior? Did the decedent seem intoxicated? These are the questions that can help answer whether or not the decedent may have died of a drug overdose.

Autopsy Findings: Expected autopsy findings in sedative/hypnotic deaths involving medications/drugs such as opioids and benzodiazepines reflect the mechanism of death, which is respiratory depression with subsequent anoxic-ischemic brain injury. They include pulmonary edema (heavy lungs), cerebral edema (a heavy, swollen brain), and urinary retention (more than 200 ml of urine). Unfortunately, these findings are not specific for a medication/drug overdose. They may not be seen in a drug overdose and they may been seen in other causes of death. In the proper clinical setting, however, these findings can support the diagnosis of a drug overdose when the blood concentrations are difficult to interpret.

Volume of Distribution: By looking at the volume of distribution of a medication or drug taken in conjunction with a decedent's weight and the amount of the drug in their blood, one can attempt to calculate in a general sense how much of a particular medication they may have taken. These calculations, however, are an estimate at best; they do not take into account pharmacokinetics, drug-drug interactions, and the whole blood to plasma ratio. As such, this technique, although potentially providing interesting information, is not recommended by the American Board of Forensic Toxicology or the Forensic Toxicology Subcommittee of the Organization of Scientific Area Committees for Forensic Science (OSAC).

CONCLUSION:

Interpretation of medication concentrations in chronic pain and hospice patients is difficult, but knowledge of the decedent's personal and medical history, as well as what they were prescribed and how they took their medications, can help the medical examiner determine the role of these medications in the person's death.

FURTHER READING:

Baselt, R. *Disposition of Toxic Drugs and Chemicals in Man,* Twelfth Edition. Seal Beach, California, Biomedical Publications, 2020.

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The Impact of Postmortem Redistribution on the Interpretation of Postmortem Toxicology Results

FINTAN GARAVAN, PHD, MD, FRCPATH (LONDON)

INTRODUCTION:

The presentation will focus on the key principles and fundamentals that are necessary to understanding when, where, or how postmortem redistribution (PMR) may have an impact on the case. The basic concepts that will be of help include information about the properties of the drug(s), the postmortem sample site, and above all, the context of the case. As with any branch of medicine, regardless of the specialty, the medical history is crucial. The more information one has about the medical history, the better chance one has of forming a reasonable opinion. The application of principles of clinical pharmacology is unsuitable to postmortem toxicology, and if done, may be very misleading. This presentation will offer advice and guidance on how to navigate through this complex subject and to avoid these common mistakes.

MAIN TEACHING POINTS:

1. Basic concepts
    1.1. Understanding why normal pharmacology principles do not apply
    1.2. Properties of drugs
    1.3. Sample site
    1.4. Postmortem interval

2. Context is critical
3. Examples
4. Tolerance

Understanding Why Normal Pharmacology Principles Do Not Apply: Any student of medicine or a science that has elements of pharmacology will recognize **Figure 1**. These are generic graphs depicting drug concentration versus time. If a blood sample is taken at specific times after ingestion, one can follow the rise and fall of the drug blood concentrations (y-axis) over time (x-axis). These graphs represent the classical blood-drug relationship over time and tell us much about the drug and its interaction with the body (half-life, absorption rate, excretion rate, etc).

However, the problem in the postmortem setting is that there are no such certainties. For example, it is not necessarily known when the drug was ingested or how much drug was ingested. For example, if one were to determine the time at which a drug was present at 1 mg/L, it would not be possible to determine which of the two places on the graph that concentration will occur (the upside or the downside).

Figure 1.

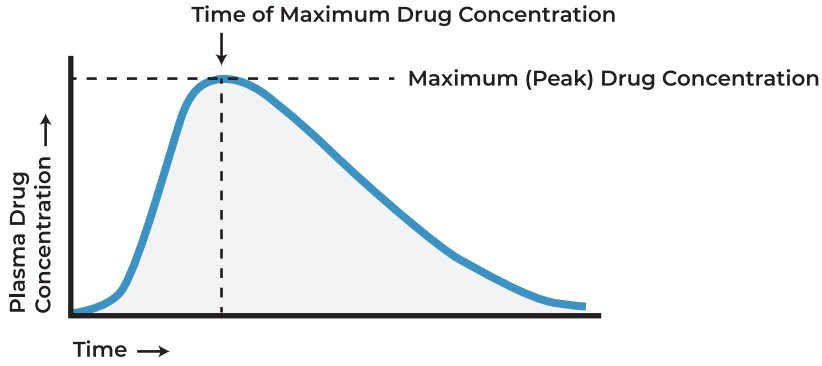

Figure 1: Taken from publicly accessible internet site located at https://www.merckmanuals.com/professional/clinical-pharmacology/pharmacokinetics/drug-bioavailability

In the postmortem setting, the opposite of what these graphs represent is the normal state. This means that rarely, if ever, will one know how much of a drug a person ingested, when it was ingested, the route, and whether they had remnants of previous drug exposure in their system. It is correct to say that in most drug-related deaths, the cause of death and the interpretation of the postmortem toxicology results are straightforward. However, it is only in a minority, albeit a very significant minority, of cases that the processes and influences of postmortem redistribution are influential. The trick is knowing which cases and what drug(s).

Properties of Drugs: Postmortem redistribution refers to changes that occur in drug concentrations within body fluids and tissues after death. Prior to the 1990s, it was thought that the interpretation of postmortem drug results was straightforward. Single blood samples were drawn, and the results were often compared to tables in books constructed from clinical studies. The interpretation of the drug was then determined from these tables as either subtherapeutic, therapeutic and/or within the toxic/fatal range. We now know that this approach is incorrect and will lead to misinterpretation(s).

The main points for consideration of whether a drug is subject to significant PMR is the volume of distribution (V_d), lipid solubility, and the Pk_a of the drug. Generally speaking, drugs with a high V_d, high degree of lipid solubility, and low Pk_a are more likely to undergo PMR. Drugs such as methamphetamine, fentanyl, clozapine, morphine, and tricyclic antidepressants are good examples.

However, it is not just these factors that are determinants. As **Figure 1** indicates; within the clinical setting where many or all factors are controlled, it is easy to follow a drug's journey within the body (pharmacokinetics) and determine how it affects that body (pharmacodynamics). Coupling this information with being able to measure body vital signs and/or observe the person, one can state with reasonable clarity that a particular drug had a particular effect or outcome.

Postmortem toxicology results cannot be assessed in this way, as we are often missing many data points and have no knowledge of the person's condition prior to death. Obtaining as much medical history and information regarding the person's normal daily activity, their regular drug use (prescribed or non-prescribed), and the scene will all provide valuable information.

Table 1 shows the loose relationship between V_d and postmortem drug concentration trends. Usually, the larger the V_d for a drug, the more likely it is that the concentration of that drug in the blood will increase after death.

Among the major influencing factors on whether a drug will be subject to redistribution is its presence or sequestration in the tissues and organs of the body. It these tissues and organs that act as the reservoir for the drug(s).

If a drug has a higher affinity for lipid than water (a high V_d) and is taken by the person over a prolonged period (many days to weeks and months) on a regular basis, stores of the drug will build up within the body. The drug will disperse and become sequestered in the solid organs, the fatty tissue, and the cellular fluids. Here, it is outside the blood vessels and not circulating or having its pharmacological effect, but it is maintained in those locations by way of natural cellular gradients. These may be physical membrane barriers or oxygen dependent ATPase gradients. It is at the time of death when these gradients fail or no longer have effect as the body is rapidly depleted of oxygen and/or the ability to maintain these gradients.

After death, the drugs that were stored or sequestered are released. They then follow a concentration gradient from the higher concentration of stored areas into the lower concentration, nonstorage areas. This is the redistribution phenomenon that starts at death and continues in an unequal and unpredictable fashion.

Table 1.

Drug	V_d (L/Kg)	Concentration trends
Diazepam	0.7-2.6	
Alprazolam	0.9-1.3	
Morphine	2-5	
Codeine	3.5	
Diphenhydramine	3-4	
Methadone	4-5	

Sampling: Every institution will have different policies regarding toxicology sampling and storage depending on their own needs, capacity, and policies. In an ideal world, it is very helpful to the toxicologist to collect more rather than fewer samples. It is recommended that both central and peripheral blood are collected (at least 5-10 mL), as well as bile, urine, gastric contents, and liver, when possible. Not every case will require such thorough sampling; however if the issue of PMR is a concern, extensive sampling may be of help.

Caution is advised when it comes to interpreting chest fluid that is often taken in a decomposing body. It is not blood, cannot be interpretated as blood, and has very limited use. Any positive results in chest fluid can indicate that a drug might have been present in the blood at the time of death or it might reflect a chronic user of a drug. In these cases, the drug re-diffuses out of tissue as the body decomposes and therefore may give a positive result with quantitation from the laboratory. Ignore the numerical result; all one can conclude is that the drug is present in the fluid. To go further in the interpretation is cavalier and overambitious.

Postmortem interval: The postmortem interval is important, but it is also a very difficult parameter to ascertain. The likelihood of obtaining central and peripheral blood samples decreases with increasing postmortem interval. Furthermore, laboratory results become less effective with higher degrees of decomposition. Each case must be taken on a case-by-case basis to address this issue.

Context: As with any field of medicine, the interpretation of information is very dependent on the context of the case. Therefore, the more that is known about the deceased person, the better. Although in practice it is not always the case that detailed information is available, efforts should be made to get as much as possible (e.g., what the person was doing in the hours or minutes prior to death; what drugs the person was known to take, either prescribed or illicit). Do an autopsy to rule competing causes (natural or otherwise). Review any scene information and any medical information that may exist. If one does not ask, one is unlikely to find out.

CASE EXAMPLE 1:

A 40-year-old woman was admitted to ER in a moribund state. She had a medical history that included severe coronary artery disease and previous suicide attempts with excess medication. She was known to have depression and was prescribed amitriptyline.

The half-lives of amitriptyline and nortriptyline are 15 hours and 22-24 hours, respectively.

Table 2.

Blood sample	Amitriptyline (mg/L)	Nortriptyline (mg/L)
Antemortem (hospital)	0.1	0.34
Femoral (hospital)	0.2	0.37
Cardiac blood (postmortem)	2.2	5.10
Gastric (postmortem)	18.0	29
Liver (postmortem)	Trace	Trace

Cause of death: Myocardial infarction due to coronary atherosclerosis

Manner of death: Natural

Comment: Assessing the ratios between a parent compound and metabolites can be useful. If the metabolite has a longer half-life than the parent compound (such as in this case) then one can form an opinion on whether the drug was ingested acutely or been taken as prescribed (in the steady state).

CASE EXAMPLE 2:

A 68-year-old man who was morbidly obese (BMI 49) was alleged to have ingested excess medications (diltiazem).

The autopsy found cardiomegaly (heart weight of 780 grams), moderate atherosclerosis of the ;eft anterior descending and right coronary arteries, severe ulcerative atherosclerosis of aorta, hepatic steatosis, and multiple white fragments in the gastric contents.

Table 3. Diltiazem Concentrations (antemortem and postmortem)

12/17/16 (23:50)	12/18/16 (16:02)	12/18/16 (20:58)	12/18/16 (23:54)	12/20/16 (Post mortem-Aorta)	12/20/16 (Post mortem-Iliac vein)
48ng/mL	570ng/mL	850ng/mL	650ng/mL	1900ng mL	2100ng mL

The typical therapeutic range for diltiazem is 100-300 ng/mL. The volume of distribution for diltiazem is 3-13 L/kg. Fatalities attributed to diltiazem have been reported at a range between 4300-33000 ng/mL.

Cause of death: Hypertensive and atherosclerotic cardiovascular disease

Other contributing conditions: Morbid obesity

Manner of death: Natural

Comment: Although there is information that this man ingested pills and that pill fragments were found in the stomach, it does not necessarily follow that the drug is responsible for the death.
The results indicate that the diltiazem never reached (in life) a blood concentration considered to be significant. There was overwhelming natural disease. The postmortem results show how diltiazem is released from stores within the body. If the postmortem result is taken in isolation, then the wrong conclusion will be drawn.

CASE EXAMPLE 3:

A 49-year-old woman was found deceased at her assisted living facility. She was known to have severe schizophrenia and was prescribed clozapine for more than 10 years at a very high dose (900 mg per day, with the maximum daily recommended daily dose being 600 mg/day). An autopsy was performed, and no anatomical cause of death was found. Blood and liver samples were retained for toxicology.

Toxicology results:

Blood (Iliac): clozapine 5.9 mg/L (therapeutic range for most patients is 0.250-0.350 mg/L)
Alcohol 6 mg%

Original Pathologist's opinion:

Medication toxicity (clozapine concentration associated with fatality)

This had been a Coroner's jurisdiction; an inquest was to be held and at that time the coroner was considering suicide as the manner of death. The family strongly objected to this as they did not believe their mother would commit self-harm and was doing very well over the prior months and years on clozapine.

Medical history:

- On clozapine for over 10 years and was taking 900 mg/day
- Admitted to the hospital on the 2nd of June with a seizure
- From the 8th to 13th of June, she was admitted to hospital for cardiac observation due a prolonged QT interval (550ms)
- On the 14th of June, her clozapine dose was reduced to 800 mg/day
- She was readmitted to the hospital on the 29th of June with another seizure
- Antemortem clozapine concentrations were never determined

Having reviewed the scene photographs and the medical history together with the autopsy findings and the toxicology report, the opinion was that the cause of death was:

Seizure disorder due to clozapine toxicity due to complications of chronic treatment-resistant schizophrenic disorder

Manner of death: Natural

Comment: Clozapine is associated with an increased risk of seizures when prescribed at 600 mg/day or higher and there is also a well-recognized and described risk of prolonged QT interval. For this patient, clozapine was prescribed at 900 mg/day for many years up to the 14th, when the dose

was reduced to 800 mg/day (still well above 600 mg/day). According to the psychiatric report, she never demonstrated signs of suicidal ideations and was coping reasonably well with her illness when compliant with her medications.

Further toxicology testing was requested on the liver. This showed a clozapine concentration of 21 mg/kg. The postmortem blood clozapine concentration (5.9 mg/L) most likely does not reflect the actual antemortem concentration and may be skewed to a higher concentration due to postmortem redistribution. Clozapine has a high V_d and is subject to PMR.

The warning signs did declare themselves when she presented with seizures. Seizures in the presence of a prolonged QT interval are significant risk factors for sudden death. It is a very remote possibility that the decedent had a prolonged QT interval prior to Clozapine treatment, and she was not known to ever have seizures until recently.

On the balance of probability, given the sudden unexpected nature of the death, the unusual position of the body at the terminal event, the urinary incontinence, and the high dosage of Clozapine therapy, it is reasonable to conclude that the manner of death is natural.

The decedent was undergoing a recognized and acceptable treatment for a natural disease that had a rare but recognized unintended side effect. In this case and according to the psychiatric expert, the ramifications of not treating her would have a far more acute catastrophic outcome.

CASE EXAMPLE 4:

A 52-year-old was beaten and kicked by attackers. He escaped and drove a few hundred meters, got out of the car, and collapsed. He was pronounced dead at the scene.

Autopsy showed blunt force injuries of the head, face, and neck (bruising and fractures of nasal bones and superior horn of thyroid cartilage), severe coronary atherosclerosis, myocardial scarring, and left ventricular hypertrophy. Histology confirmed the above. Blood from the iliac vein contained methamphetamine at 0.6 mg/L and THC was present.

Two individuals were charged with murder. The defense argued their client's actions did not kill the decedent, but rather, that the methamphetamine did.

Medical history: The decedent was a heavy methamphetamine user. On the day of the incident, he was lying on a couch watching a TV show when the accused knocked at the door. The assault then took place. He ran from the scene about 100 yards before collapsing and was pronounced dead at scene.

Cause of death: Coronary atherosclerosis

Other contributing conditions: Blunt force head and neck trauma, Chronic methamphetamine use

Manner of death: Homicide

Comment: Obtain as much information as possible about the case including medical history and the last known movements/activities of the decedent. Learn the normal habits (prescribed and/or non-prescribed drug use) of the decedent. To understand how someone dies, understand first how they lived.

CONCLUSION:

1. Review the information from the scene of death (as much as there is to review).
2. Learn as much about the decedent as possible.
3. Review medical history and notes.
4. Rule out competing causes of death at autopsy.
5. Take at least two blood samples: one central and one peripheral.
6. Consider whether examining drug ratios could be useful.
7. Consider the properties of each drug.
8. Has the decedent been taking this drug for a long time?
9. Each case must be taken in context.

FURTHER READING:

Yarema MC and Becker CE. Key concepts in postmortem drug redistribution. *Clin Toxicol* 2005; 43(4):235-241. PMID: 16035199.

CHAPTER SEVEN

Effects of Scheduling on the Rise of Novel Synthetic Opioids from Fentanyl to its Analogs to the Nitazenes

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INTRODUCTION:

Forensic Pathologists rely on accurate, timely toxicological data to make findings as to medical diagnosis and determination of cause and manner of death. The rapid emergence of novel psychoactive substances (NPS), coupled with the short lifecycle of those substances, makes timely and accurate identification of the substances extremely challenging, but nonetheless crucial for the accurate certification of drug caused and related deaths. While various forms of NPS have been in existence for decades, the dawning of the fentanyl analogue era in late 2015 with its steep rise in deaths severely impacted medicolegal death investigations. The injurious and deadly impacts continue today with the rise of "Next Gen" opioids, such as the benzimidazoles and other very novel opioids.

The rapid fentanyl analogue proliferation of 2016-2018 brought about the innovative and successful Drug Enforcement Administration (DEA) action of temporary scheduling of fentanyl-related substances by class or by core molecular structure. The class or core molecular structure approach to scheduling used with fentanyl-related substances could potentially be used by the DEA again to temporarily schedule nonfentanyl opioids, such as the benzimidazoles, sometimes referred to as "the nitazenes," by class or core

structure. The administrative processes associated with fentanyl-related substance scheduling have revealed, however, that permanent scheduling of fentanyl-related substances or of any cohort of substances by class or common molecular structure is highly unlikely due to the U.S. Department of Health and Human Services (DHHS) determination that medical and scientific evaluation of substances by class or core structure cannot be scientifically conducted.

The morbidity associated with fentanyl analogues and the current upward-trending of nonfentanyl opioid deaths demonstrates that public health and public safety stakeholders continue to be challenged by the morbidity and mortality associated with these deadly emerging substances. Sharing of all information known about a novel substance's chemical composition, potency, prevalence, polydrug combinations in toxicological samples and seized drugs, and geographic distribution of substances must be a critical part of a national strategy for preventing overdoses and deaths. Timely, open access sharing of that body of information not only provides the DEA with tools to quickly enact temporary scheduling of qualifying substances, but also provides valuable "pointer" information on a substance's geographic spread, polydrug co-occurrence, and other important factors. The illicit opioid era has demonstrated the compelling need for research and open-source data and information dissemination between governmental and nongovernmental partners, the medicolegal death investigation community, and forensic scientists. The Center for Forensic Science Research and Education (CFSRE's) NPS Discovery Program successfully demonstrates the importance of collaboration and data sharing to both aid the DEA in rapidly issuing scheduling actions, and to rapidly provide actionable scientific information on new substances to public health and public safety partners.

MAIN TEACHING POINTS:

1. Forensic Pathologists rely on accurate, comprehensive, and timely identification of novel psychoactive substances and drugs of misuse to make determinations as to cause and manner of death.

2. The difficulties in identification of fentanyl analogues in 2016 and 2017 foreshadowed the current challenges in identification and understanding of benzimidazoles and other novel synthetic opioids, designer benzodiazepines, novel stimulants, hallucinogens, and other substances of first-instance identifications. Emerging novel substances frequently evade detection due to the short lifecycle of the new substances in the

drug supply, the lack of analytical standard reference materials needed for exact scientific identification, and the lack of resources needed to consistently perform the extensive NPS toxicological testing needed to identify these novel drugs.

3. Specific identification of newly emerging substances such as the nitazenes, which have demonstrated and proven morbidity, mortality, and seizure prevalence, is important to public health and to public safety, and primacy must be placed on scientific and professional collaboration to rapidly obtain and freely share such information.

4. A primary source for obtaining relatively immediate information about novel substances is the NPS Discovery program operated by the CFSRE. NPS Discovery (www.npsdiscovery.org) is a free open access national drug early warning system that combines analytical characteristics, research findings, authentic case histories, and surveillance and monitoring strategies, all of which support early detection, harm reduction, treatment, and forecasting of new drug trends.

5. Another important source for obtaining information on identification, chemical composition, morbidity, mortality, and prevalence are the DEA's administrative documents entitled *Notice of Intent and Notice of Scheduling of Substances.* The DEA issues those public notifications when it has determined that a particular substance poses an imminent hazard to public health and safety. While scheduling of substances is largely perceived as a law enforcement and prosecutorial tool to jail offenders more easily, that perception overlooks the public health informational utility in the DEA scheduling notices. The DEA utilizes reliable sources of information, such as NPS Discovery, data from other research labs, and mortality data voluntarily supplied by medical examiners and coroners to produce a comprehensive overview from which prevalence, potency, geographic location, and mortality can be determined.

6. Fentanyl analogues resulted in extremely significant morbidity and mortality in 2016 and 2017. Fentanyl analogues were identified with increasing rapidity in 2017, yet evolution outpaced identification. After fentanyl-related substances were placed on the temporary schedule by DEA in 2018 (which was followed by the scheduling of fentanyl- related substances by China), the appearances of new fentanyl analogues went into decline. The exact sequence of events that caused changes in

manufacturing and distribution is unknown, but the pattern of drugs declining in positivity following scheduling was repeatedly demonstrated as was the disappearance of whole classes of drugs following the institution of core structure scheduling.

7. With the demise of fentanyl analogues, a new generation of novel opioids appeared and proliferated. 2-benzyl benzimidazole analgesics, commonly referred to as the nitazenes, came into prominence beginning in 2019. Isotonitazene was the first in this series and had a relatively lengthy and deadly lifecycle of nearly a year. As the prevalence of isotonitazene waned, brorphine, metonitazene, N-pyrrolidino etonitazene, and others have come into prominence.

8. Benzimidazoles belong to a chemical family that would potentially enable the DEA to temporarily schedule them by core structure or class as was done with fentanyl-related substances.

9. The decision to temporarily schedule by class or core molecule lies within the sole discretion of the DEA. Permanent scheduling of substances, however, is a collaborative process between the Department of Health and Human Services (DHSS) and the DEA, with DHHS having the final decision. DHHS officials have testified in Congress that they are practically and scientifically unable to perform the requisite scientific and medical evaluations that must precede permanent scheduling for an undefined class of substances such as fentanyl analogues. DHHS is, therefore, unwilling to place entire classes of substances on a permanent schedule. Whether the DEA will ever again undertake temporary scheduling of a class of substances by core structure as it did with fentanyl analogues is unknown in light of DHHS' pronouncement of its unwillingness to consider permanent class-based scheduling for entire classes of substances.

ANALYSIS:

The emergence of fentanyl analogues foreshadowed the rapidly evolving opioid, fentanyl, and nonfentanyl opioid crisis:

The opioid crisis of the past two decades manifested through deaths and overdoses related to the use of heroin and misused prescription opioids in the early years of the 2010 decade. While public health and law enforcement believed that the overdose deaths numbers were soaring to unimaginable levels in those years, the opioid era was only beginning.

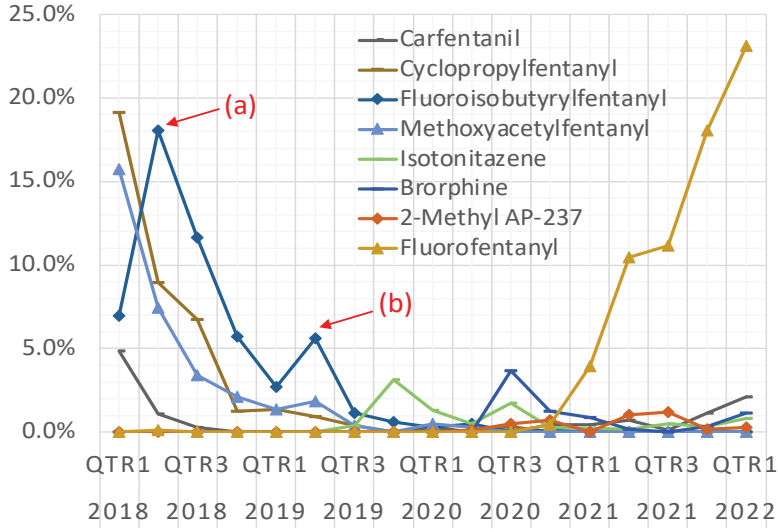
In 2015, 2016, and 2017, deaths by various analogues of illicit fentanyl began to appear on death certificates. The illicit fentanyl analogues infiltrated the legacy drug supply through deliveries from international express mail shipping consignment conveyances and international mailing facilities. At the height of the analogue influx, fentanyl analogues were appearing at a rate of several per month. These substances generally exhibited a short lifecycle before being replaced by another new fentanyl analogue thereby frustrating attempts by forensic laboratories to keep up with fentanyl analogues identifications and testing.

The challenges and difficulties of identifying novel cannabinoids, cathinones, stimulants and novel opioids and benzodiazepines preceded the fentanyl analogue era, but the mortality of the fentanyl analogue surge brought the need for identifications into sharp contrast and relief. The overdoses and deaths caused by fentanyl analogues in clinical settings and postmortem toxicology and the prevalence of fentanyl analogues in drug seizure testing spurred an emergent focus on the rapid evolution and need for identification of the deadly fentanyl analogues. To meet that compelling need, the CFSRE established the NPS Discovery program in 2018. NPS Discovery, which is an open-access, freely accessible national drug early warning system for the United States, will be discussed at length later in this paper. The work done by the NPS Discovery team on tracking the evolution of novel opioids and the importance of emergently obtaining identifications, information and data on those substances formed the basis of this presentation and its conclusions discussed herein.

The graphs on the following page document the emergence and lifecycle of various emerging substances causing significant morbidity and mortality between 2016 and Quarter One 2022.

Figure 1.

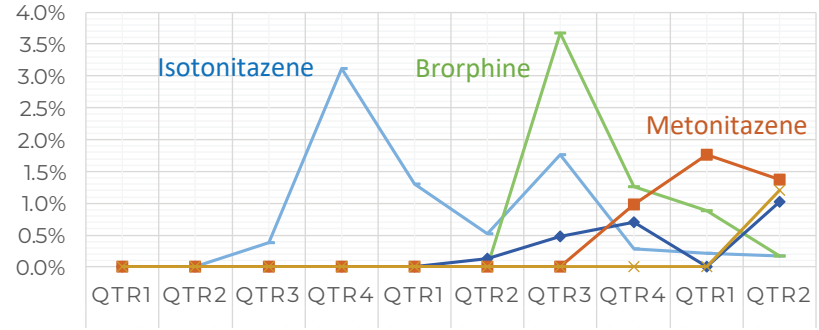
Fentanyl Analog Positivity in NMS Labs Postmortem Blood 2016-2022



(a) Q1 2018 is U.S. Temporary Scheduling of Fentanyl-Related Substances
(b) Q2 2019 is China scheduling of Fentanyl-Related Substances by Class

Figure 2.

Novel Synthetic Opiod Positivity in NMS Labs Postmortem Blood 2016-2021



Emergence of benzimidazole ("nitazene" class) Novel Synthetic Opioids in NMS Labs postmortem toxicology casework 2019 - 2021

The Nitazenes—The Next Generation of Illicit Synthetic Opioids:
Benzimidazole analgesics, commonly known as the nitazenes, came into prominence beginning in 2019. Nitazenes did not begin as illicit substances manufactured in in foreign laboratories. In 1958, U.S. Patent 2.944,062 for this class of substances was issued to scientists at Ciba Pharmaceuticals in New Jersey. Beneficial properties for the substance included analgesic and muscle relaxation effects. The substances were found to be particularly effective with a nitro substitution at R2, and a lower alkoxy group at R1. Etonitazene was found to be 60 times the potency of morphine in humans.

There was a general awareness of the benzimidazoles in the late 1990s with clandestine laboratories being identified from Germany and Poland. In 2003, a clandestine lab in a US chemical company in Utah that was manufacturing illicit 2-Benzyl Benzimidazole analgesics was taken down. Chatter in online forums about this drug class ticked upward in 2005 and continued to gain prominence as time passed. The first death associated with benzimidazoles in North America was reported in Alberta, Canada in 2019. Isotonitazene was found to be the cause of toxicity death, with metonitazene also detected in paraphernalia. The current prevalence, morbidity, and mortality of the benzimidazoles warrants a detailed analysis of the individual benzimidazoles currently in circulation beginning with isotonitazene.

Isotonitazene emerged in toxicology and seized drug samples in the United States and Canada in 2019. *In vivo* animal models suggest isotonitazene is from two to six times more potent than fentanyl. Its N-desethyl metabolites, however, have been found to be significantly more potent than fentanyl.

In a CFSRE publication entitled *Isotonitazene Quantitation and Metabolite Discovery in Authentic Forensic Work*, 150 postmortem samples were identified as positive for isotonitazene, with quantitation performed on 116 of those samples. Blood concentrations ranged from 0.19-39 ng/ml, with a mean/median of 1.88+4.2 ng/ml/0.94 ng/ml. In the study, isotonitazene was most commonly found in combination with flualprazolam (69%) and etizolam (25%). In half of the cases, however, isotonitazene was the only opioid detected. The cause of death was typically single or multiple drug intoxication and manner of death was typically found to be accidental. Isotonitazene was initially detected in toxicology samples from Illinois, and then the substance rapidly proliferated throughout the Midwest and ultimately infiltrated 23 states. Mortality rates associated with isotonitazene increased in number through April 2020.

The Drug Enforcement Administration published a Notice of Intent to Schedule Isotonitazene to Schedule I on November 4, 2021, after making findings that the substance constitutes an imminent hazard to public safety. By the time isotonitazene was officially placed on Schedule I under the DEA's temporary scheduling authority, the next illicit opioid commonly named brorphine had appeared.

Brorphine (Benzimidazol-2-one) was evaluated as a class for medical and pharmacological efficacy in the 1960s. *In vitro* studies suggest brorphine has a potency similar or slightly less than fentanyl. In the CFSRE publication entitled *Brorphine – Investigation and Quantitation of a New Potent Synthetic Opioid in Forensic Toxicology Casework Using Liquid Chromatography-Mass Spectrometry,* findings were made relating to 20 postmortem cases. Brorphine was most commonly found in combination with flualprazolam (50%) and fentanyl (100%). Brorphine was also found in combination with ethanol in postmortem samples.

Multiple drug intoxication was the most common cause of death in brorphine cases, and manner of death was generally found to be accidental. Brorphine blood concentrations were as follows: Blood, 2.5+3.1 ng/ml, with a median of 1.1 ng/ml and concentrations ranging from 0.1-10 ng/ml. Brorphine urine concentrations were as follows: 4.6+7.6 ng/ml, with a median of 1.6 ng/ml and concentrations ranging from 0.2-23 ng/ml. Like the emergence of isotonitazine, brorphine first appeared in postmortem samples in Illinois. The substance spread through the Midwest and was ultimately detected in eighteen states. Brorphine mortality increased through September 2020. The DEA published its Notice of Intent to Schedule brorphine on the temporary schedule in December of 2020; however, brorphine's lifecycle had largely ended in October 2020. Brorphine was replaced in the market by the rise in prevalence of another benzimidazole called metonitazene.

Metonitazene, like isotonitazene, is a member of the benzimidazolone class. It was described in a patent in 1958 but only achieved popularity in the United States in 2020 as isotonitazene and brorphine began to decline. As described in the patent, metonitazene and etonitazene produced the greatest amount of respiratory depression in animal models, with respiratory depressant effects estimated to be 50 times more potent than morphine in one particular model, although there was conflicting data in other animal models. In postmortem samples, metonitazene was the sole drug of interest in 15% of the cases, and was the only opioid detected in 30% of the case. Metonitazene was found

most commonly with fentanyl (50%) and novel benzodiazepines, including etizolam, flualprazolam, and pyrazolam. The cause of death in metonitazene related deaths was multiple drug intoxication and the manner of death was typically deemed accidental. Metonitazene concentrations were as follows: 6.3+7.5 ng/ml, with a median of 3.8 ng/ml and concentrations ranging from 0.5-33 ng/ml. Metonitazene concentrations in urine were as follows: 15±13 ng/ml, with a median range of 0.6-46 ng/ml. Metonitazene appeared in postmortem toxicology cases in the United States beginning in November 2020, with an acceleration in positivity in February 2021. Metonitazene remains the most common benzimidazole detected as of Spring 2022.

The year 2021 brought the emergence of a proliferation of new benzimidazole analogues, including N-pyrrolidino etonitazene, etodesnitazine, protonitazene, metodesnitazine, butonitazene, and flunitazene. N-pyrrolidino etonitazene was the most popular of this series and has shown some evidence of displacing metonitazene as we enter the Spring of 2022.

As 2022 progresses, increasing incidences of cinnamylpiperazines are now also being detected, even while the benzimidazolones continue to be present. The substances that have been identified in the class that includes AP-237, 2-methyl AP-237, and AP-238. These substances bear similarity to the MT-45 class of substances and they primarily affect the mu-opioid receptors but are substantially less potent than other novel synthetic opioids described above. AP-238 is more potent than 2-methyl AP-237 and AP-237, but less potent than fentanyl by a factor of 11. The cinnamylpiperazines also have lower toxicity in animal models than morphine. Two postmortem case studies involving AP-238 revealed a wide differential in blood and urine levels. Postmortem Case Study One involved blood levels of 87 ng/ml and urine levels of 120 ng/ml, with polydrug findings of 8-aminoclonazolam, methadone, memantine, and delta-9-THC and metabolites. Postmortem Case Study Two involved blood concentrations of 270 ng/ml and urine levels of 1200ng/ml, with polydrug findings of 8-aminoclonazolam, flualprazolam, and Delta-9-THC and metabolites. Cause of death was listed as drug toxicity with specific reference to AP-238 in both cases.

Potential Permanent Class or Core Molecule Scheduling of Benzimidazoles –Possible, but Improbable Based on Agency Action Toward Fentanyl-Related Substances: Benzimidazoles could be placed in Schedule I on a temporary basis as a class upon a finding by the DEA that they pose an imminent threat to public safety. Three members of this drug class have

notable mortality that is proven to be associated with the substance, thereby providing a factual basis for consideration of for scheduling the class of benzimidazoles.

The original patent describing the benzimidazole pharmacology identified a core structure and noted that the class encompassed analogues with substitutions at various moieties in key positions, R1 and R2. The inventors also noted that nitro substitution on position R2, and alkoxy substitution on R1 were particularly effective in in their analgesic properties. The information contained in the foregoing review of the identified benzimidazoles relating to morbidity, mortality, and prevalence of the nitazenes would certainly seem to support proceeding through class scheduling for benzimidazoles modeled on the DEA's February 2018 temporary class scheduling of fentanyl-related substances. The lessons learned from the fentanyl-related substance scheduling processes, however, are instructive of the political and societal challenges and potential objections raised to scheduling of substances by class.

As stated, the benzimidazoles have a molecular composition that would support temporary scheduling by class or core molecule structure. In light of the deaths associated with the several members of the class, scheduling by class would be a facially reasonable choice. The successful fentanyl-related substance scheduling by class was not, however, only based on reason. The innovative step of scheduling by class was taken as fentanyl analogues multiplied and escalated leaving unprecedented death in their wake. While more reactive scheduling of individual fentanyl analogues continued, agencies struggled to keep pace, with testimony in Congress comparing fentanyl analogue appearances and scheduling to the "whack-a-mole" game (see *Congressional Hearing in the Committee on the Judiciary, Subcommittee on Crime, Terrorism and Homeland Security January 28, 2020, testimony of DHSS Admiral Brett P. Giroir*).

Review of DEA Scheduling Action Notices published in the Federal Register in 2016, 2017 and 2018 demonstrate the public health and public safety threat posed by the rapidly evolving fentanyl analogues. By the time the Notice of Intent to Temporarily Schedule furanyl fentanyl into Schedule I was published on September 27, 2016, 128 deaths in five different states were associated with the furanyl fentanyl analogue. The Notice of Intent to Schedule Acryl Fentanyl temporarily was published on July 14, 2017. By the time the Notice of Intent posted, 83 associated deaths in five states had occurred, and acryl fentanyl had been seized in 19 states. When the Notice

of Intent to temporarily schedule cyclopropyl fentanyl was published, there had already been 115 associated deaths in five states. Those extremely high mortality rates, coupled with the public's anxiety and fear around the rapidly evolving drug threat, represented an unprecedented public health and public safety emergency.

Against that backdrop, the DEA issued a Notice of Intent to schedule fentanyl-related substances in December of 2017. The agency subsequently issued the Notice of Temporary Scheduling of Fentanyl-Related Substances into Schedule I of the Controlled Substances Act on February 8, 2018. The exact language of the Scheduling Notice reads as follows, in pertinent part:

> *When the temporary scheduling order is issued, fentanyl-related substances will be placed in schedule I of the CSA for two years. DEA may extend the temporary scheduling for an additional year (a total of three years) if proceedings to permanently schedule the substances are pending. DEA's intention is that the temporary scheduling order will define fentanyl-related substances to include any substance not otherwise controlled in any schedule (i.e., not included under any other Administration Controlled Substance Code Number) that is structurally related to fentanyl by one or more of the following modifications:*
>
> *(A) Replacement of the phenyl portion of the phenethyl group by any monocycle, whether or not further substituted in or on the monocycle;*
> *(B) Substitution in or on the phenethyl group with alkyl, alkenyl, alkoxyl, hydroxyl, halo, haloalkyl, amino or nitro groups;*
> *(C) Substitution in or on the piperidine ring with alkyl, alkenyl, alkoxyl, ester, ether, hydroxyl, halo, haloalkyl, amino or nitro groups;*
> *(D) Replacement of the aniline ring with any aromatic monocycle whether or not further substituted in or on the aromatic monocycle; and/or*
> *(E) Replacement of the N-propionyl group by another acyl group.*

In summary, the temporary scheduling order defined fentanyl-related substances as any substance that is structurally related to fentanyl by one or more of five chemical modifications and is not otherwise controlled in any schedule. Under the DEA's definition and parameters for fentanyl-related substances, core chemical composition is the only requirement for scheduling. There is no requirement that fentanyl analogues have fentanyl-like pharmacological activity, which became a problematic issue in the agency dialogue relating to permanent scheduling of fentanyl-related substances as a class.

Two important points included in the DEA's Notice of (Temporary) Scheduling Order also should be noted, as these points were also probative of DHHS' subsequent refusal to permanently schedule fentanyl-related substances administratively:

1. *The DEA will (and has) continued to schedule fentanyl analogues by specific chemical name once identified, even if those substances were included in the fentanyl-related substances class, and*
2. *the scheduling order applies to fentanyl-related substances that have already been discovered and identified, and it also applies to fentanyl analogues that fit within the definition that have yet to be created or developed.*

The question arose during the presentation of the Grand Rounds session as to the DEA's authority to temporarily schedule fentanyl-related substances. The DEA is solely empowered under 21 United States Code Section 811(h) and Code of Federal Regulation Section 1308.49 to temporarily place a substance into Schedule I on a temporary basis if it determines that such action is necessary to avoid an imminent hazard to the public safety. The factors used by the DEA to determine whether a substance poses an imminent hazard are set forth in 21 United States Code, Section 811. Those factors include the substance's history and pattern of abuse, the scope, duration and significance of abuse, and any risk the substance poses to the public health. Congress has specifically stated that in making their determination, the DEA can assess actual abuse of the substance, diversion from legitimate channels, and clandestine importation, manufacture, or distribution.

Temporary scheduling by the DEA is an agency action that is conducted as an administrative "notice and comment" rulemaking. The process commences once a substance has been identified and is associated with sufficient morbidity, mortality, and seizures to pose an imminent hazard to public safety. The DEA provides a 30-day notice to the Secretary of Health and Human Services stating the factual basis for the proposed temporary scheduling and makes formal inquiry of DHHS as to whether there are pending investigational drug applications or approved new drug applications for the identified substance. The DEA also conducts independent investigation in medicolegal death investigation and law enforcement communities on morbidity, mortality, seizure data, geographic prevalence and spread, international and state scheduling, and other factors that relate to the threat posed by the substance and the lack of currently accepted known medical value of the substance.

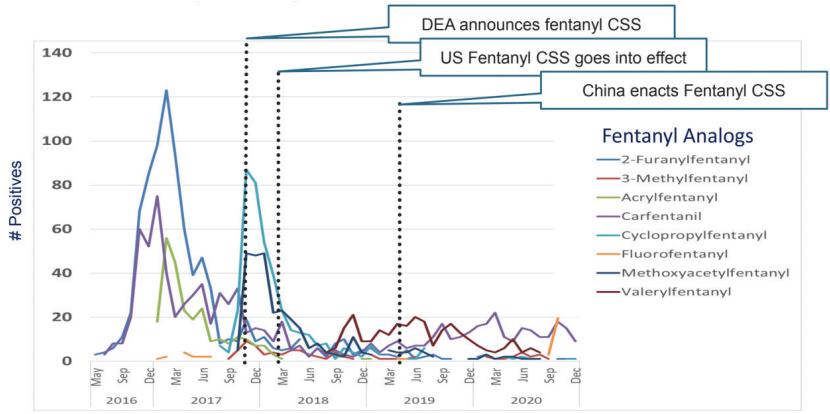
If the DEA's research and investigative processes lead to a decision to temporarily schedule a substance, the DEA issues a formal Notice of Intent to Schedule which is published in a federal government publication known as the Federal Register. A period of Notice and Comment follows. If the DEA determines that the substance should be temporarily scheduled, the agency publishes a Notice of Placement of the substance into Schedule I. The period of placement under temporary scheduling authority is two years; however, that period of placement on Schedule I can be extended by an additional year if DHHS and FDA are actively engaged in the medical and scientific evaluations of the substance that is required as part of the permanent scheduling process.

The DEA's use of temporary scheduling protocols to schedule fentanyl-related substances as a class was noteworthy and subject to skeptical questioning under the plain language of 21 United States Code, Section 811(h) which reads, *"If the Attorney General [as delegated to the DEA by Department of Justice protocols] finds that the scheduling of a substance in schedule I on a temporary basis is necessary to avoid an imminent hazard to the public safety…"* (Emphasis added). Challenge was expected as to whether fentanyl-related substances were "a substance"; yet, no public acknowledgement of challenge, if any, was made known during the period of administrative temporary scheduling of fentanyl-related substances or referenced in public comment.

As was commented upon during the Grand Rounds presentation, no "but-for" causation can be shown between the significant decline of fentanyl analogues in 2018 and the timing of the publication of DEA's Notice of Intent to Schedule Fentanyl-Related Substances (11.2017), the DEA's scheduling of those substances (02.2018) and China's scheduling of fentanyl-related substances by class (05.2019). Objective data exists, however, to demonstrate a strong correlation between the scheduling actions and the decline of fentanyl analogues detection in postmortem identifications and seizures. The diagram directly below visually represents the reduction and near extinction of fentanyl analogues as represented by NMS Labs' postmortem testing data which correlates to core structure scheduling actions in the United States and in China.

Figure 3.

NMS Labs Fentanyl Analog Positivity 2016-2020



Additionally, the General Services Administration report entitled, *"Synthetic Opioids: Considerations for the Class-Wide Scheduling of Fentanyl-Related Substances"* published in April 2021 states the following information:

> *….[o]n the basis of its laboratory information system data and other sources, DEA identified 26 new fentanyl analogues from 2016 through January of 2018 and 12 new fentanyl analogues after class-wide scheduling as of July 31, 2020. DEA notes that many of the new fentanyl analogues identified in 2016 and 2017 were encountered at high rates compared to the new analogues identified after class-wide scheduling. For example, DEA laboratory information system data show there were 2,149 law enforcement reports of acryl fentanyl in 2016 and 2017, which was more than four times the total number of reports for all 12 new fentanyl analogues identified after class wide scheduling….*

The General Accounting Office (GAO) Report also discussed the potential effects of China's class wide scheduling of fentanyl analogues in May of 2019, stating:

> *Our analysis of CBP (Customs and Border Protection) seizure data shows that the number of seizures of fentanyl and its analogues entering the United States from China decreased from 352 seizures in fiscal year 2018—before the announcement [from China]—to 10 seizures in fiscal year 2020 through July.*

While correlation is admittedly not equivalent to causation, data provides probative circumstantial evidence indicating fentanyl-related class scheduling in the United States and in China contributed to the dramatic decline in fentanyl analogues.

Temporary administrative scheduling of fentanyl-related substances expired in February 2020; two years after the scheduling order took effect. Fentanyl-related substances are only now remaining on Schedule I in a temporary status due to Congressional intervention, with the Congressional "fix" now set to expire on December 31, 2022. Permanent scheduling of fentanyl-related substances by administrative agency or by Congressional action appears unlikely even though temporary scheduling of fentanyl-related substances reportedly had positive results and impacts for public safety.

Unlike temporary scheduling of substances upon a finding of imminent hazard to public safety which lies in the sole discretion and authority of the DEA, permanent scheduling of substances requires a collaborative process between DHHS and the DEA. Before the DEA can initiate a rulemaking to permanently schedule a substance, the DEA must request a scientific and medical evaluation of the substance from DHHS and its Food and Drug Administration. The DHHS medical and scientific evaluation must consider the three factors considered for temporary scheduling (Factors 4, 5 and 6 *immediately below*), but it also must consider a host of other factors set forth at 21 United States Code, Section 811(a)-(c). Those factors, which comprise the elements of the process commonly known as "The Eight Factor Analysis" for permanent scheduling, are:

1. *The substance's actual or relative potential for abuse;*
2. *Scientific evidence of its pharmacological effect, if known;*
3. *The state of current scientific knowledge regarding the substance;*
4. *The substance's history and current pattern of abuse;*
5. *The scope, duration, and significance of abuse;*
6. *Any risk the substance poses to the public health;*
7. *The substance's psychic or physiological dependence liability, which refers to the potential for users to become psychologically or physically dependent on a substance; and*
8. *Whether the substance is an immediate precursor of an existing controlled substance.*

Once the mandatory medical and scientific evaluations are completed and the FDA has analyzed the substance proposed for scheduling under the Eight Factors, DHHS decides whether the substance should, or should not, be scheduled. DHHS is the sole and final decision maker as to the permanent scheduling decision.

As the opioid crisis and fentanyl proliferation came before Congress in 2020 and 2021, DHHS representatives were called upon to discuss the permanent scheduling of fentanyl-related substances. In Congressional hearing held in April of 2021, high-ranking officials from DHHS testified that, *"[a]nalyzing a class of substances rather than individual substances would be a change for HHS and that it may not be feasible…"*. By the time officials from DHHS provided Congressional testimony in December 2021, Dr. Douglas Throckmorten, Deputy Director for Regulatory Programs–Center for Drug Evaluation and Research in DHHS testified that the Eight Factor analysis for fentanyl-related substances by class was not completed and would not be done.

Dr. Throckmorton advised that DHHS had determined that the statutory Eight Factor Analysis with its integrated medical and scientific evaluations could not be conducted on the class of fentanyl-related substances because of the following considerations: a) the vastness in number of hypothetical substances covered, b) the pharmacological and epidemiological data showing harms and overdose deaths were available for fewer than 30 fentanyl-related substances, and c) among the individual fentanyl-related substances for which pharmacological activity has been studied, the FDA has identified examples of substances lacking mu-opioid agonist activities, therefore, the presumed potency pharmacology would incorrectly lead to the conclusion that the substances pose opioid-related harm. Based on DHHS' reasoning and justification as to the agency's inability to perform scientific and medical evaluations on classes of substances, the logical conclusion is that permanent scheduling of the benzimidazole class or any class of substances with a core molecular structure will not occur.

Congress passed the Temporary Reauthorization and Study of the Emergency Scheduling of Fentanyl Analogues Act with the Act signed into law in February 2020. The Act was set to expire on May 6, 2021. On May 4, 2021, extension was granted until October 22, 2021. On September 20, 2021, the Act began moving with Appropriations bills that were being approved in Congress to avoid governmental shutdown. The Act has never been extended in Congress based on consideration of merits and content of the legislation. The Act

providing for scheduling fentanyl-related substances as a class was again extended to December 3, 2021, and then to January 18 and February 22, 2022 as it moved in omnibus bills. With the passage of the Appropriations Bill in March 2022, the expiration of the Act providing for fentanyl-related substances scheduling is extended until December 31, 2022.

Public Health Clues and Collaborations Emerging from Temporary Scheduling Processes, Rather Than Outcomes: The temporary scheduling of fentanyl-related substances by class may never lead to permanent scheduling of fentanyl analogues by administrative or legislative means. Whether fentanyl analogues will re-emerge is a question for the future, as is the question of whether the DEA will ever again utilize temporary scheduling of substances by class. Much has changed since the fentanyl analogues were appearing at a pace of one to two identifications per month. Illicit fentanyl is the relatively cheap, potent killer of concern, with over 108,000 predicted overdose deaths in the twelve-month provisional period from February 2021 to February 2022 according to CDC's Provisional Drug Overdose Data. Nonfentanyl opioids such as isotonitazene, metonitazene, and the AP-series are contributing to deaths, but those substances lack the direct attributive alarm relating to overdose deaths that the fentanyl analogues carried. The overdose mortality world is one of polydrug combinations, cocktails, and counterfeit pills.

One can argue, however, that the societal gains and benefits from fentanyl-related substances' temporary scheduling resulted as much from the learning processes and increasing collaborations that were strengthened in the temporary scheduling process as from the fentanyl-related scheduling action itself. One need only look at the Notice of Intent to Schedule Isotonitazene published on June 18, 2020 to understand how the scheduling process has become expedited, tightened, and partner-informed, and is now a "virtual pointer" to the emergence of novel substances.

Unlike the fentanyl analogue era when hundreds of people died before a substance was scheduled, more rapid identifications of substances allow investigation into and compilation of data and information about the substances. When the Notice of Intent to Schedule Isotonitazene was published, only 18 deaths in four states were associated with that substance. One state was reporting a presumptive identification of isotonitazene in an overdose death and one state identified a single overdose that occurred between August 2019 and January 2020. Similarly, the Notice of Intent to

Schedule issued after only eight law enforcement encounters had occurred in in two states. By the time the Scheduling Notice issued after the notice and comment period had elapsed, the number of seizures increased to 48 seizures in five states. Nevertheless, the rapidity of isotonitazene scheduling inferentially demonstrates that when contemporaneous and immediate awareness of the morbidity, mortality, and prevalence data is linked to the rapid identification of substances, more rapid scheduling of substances by the DEA can occur.

Temporary scheduling notices, including the Notice of Intent to schedule a substance and the Scheduling Order temporarily scheduling a substance contain a wealth of information about respective newly emerging substances. In addition to morbidity and mortality data and information, the Notice of Intent to Schedule often includes pharmacological profiles, chemical profiles, potency information (if known), the results of FDA inquiry as to pending drug applications for the substance, and the international profile, prevalence, and scheduling status for the substance. The notifications detail the forms in which the substance has been found, such as pills, tablets, liquids, and counterfeit pills. The polydrug combination in which the substances have been encountered in toxicology and seized drug testing is featured, providing probative intelligence for medicolegal, public health, and public safety communities. For instance, the isotonitazene scheduling notice states that the substance had been found in California mixed with the legacy drug heroin and the illicit benzodiazepine bromazolam. The information in scheduling notices can, therefore, be used as pointers or clues as to whether a substance is a causative factor in overdoses and overdose deaths in particular localities and states.

The rapid evolution, proliferation, and associated morbidity and mortality associated with fentanyl analogues and the upward trending of nonfentanyl opioids have brought to light the great importance of collaboration and open-source sharing and dissemination of the most exact, timely, and comprehensive technical and data and information on novel substances as they emerge.

Researchers specializing in NPS identifications and influences have proven critical to the free and open sharing of information to the public health community. The Center for Forensic Science Research and Education's (CFSRE's) NPS Discovery Program (NPSDiscovery.org) is a free, open-access platform on which all the information in Dr. Logan's portion of this Grand Rounds presentation can be found along with scientific, technical, trend and

policy data on many other novel illicit opioids, stimulants, hallucinogens, benzodiazepines, and toxic adulterants.

The leaders at NPS Discovery gather intelligence about new substances through national and international data, literature and patents, surface and dark web monitoring, collaboration, information sharing with governmental and private collaborators, and trend data compiled from in-house testing and research. Surveillance and monitoring activities continue as novel substances from clinical, postmortem, and seized drug samples are tested by the scientists in the CFSRE laboratory. NPS Discovery leaders then directly respond to partners in need of specific information and answers, and also issue myriad publications, including scientific monographs, public health alerts, clinical reports, NPS scope of testing recommendations, trend reports, quarterly reports, and NPS toolkits.

When partnerships are formed between governmental and private partners in the service of public health and public safety at local, state, national and international levels relating to emerging novel substances, awareness and knowledge of the morbidity and mortality associated with emerging substances and threats posed by the substances is accomplished, regardless of the scheduling status of substances.

CONCLUSION:

Although small in number relative to the number of fentanyl deaths, non-synthetic opioids are now associated with overdose deaths throughout most of the United States. Accurate and timely identification of the exact substance has proven to be critical to determining cause of death. The rise of illicit fentanyl analogues has now given way to nonfentanyl opioids and illicit fentanyl which all have individuated degrees and levels of receptor activity and attendant dangers. The major nonsynthetic opioids currently impacting medicolegal death investigation communities are metonitazene, N-pyrrolidino etonitazene, and 2-methyl AP-237, but the trending of novel substances is continually changing and evolving. Illicit drug markets are very dynamic, with nonsynthetic opioids contributing to many polydrug deaths. Temporary scheduling of such substances, which is based on compilations of data and information on morbidity, mortality, and substance prevalence, may be a probative public health tool, providing "virtual pointers" for laboratories, forensic pathologists, and clinicians. The rapid and continual evolution of novel substances such as opioids, designer benzodiazepines and other NPS manifests in polydrug toxicology and seized drug testing. While government

actions such as scheduling notices provide valuable information, those highly vetted governmental processes cannot stand alone in the effort to inform and assist public health. Open-access platforms and sites such as CFSRE's NPS Discovery provide open-source, contemporaneous, scientifically validated data and information that can provide significant added value to the public health mission performed in medicolegal death investigation communities.

DISCLOSURES:

Dr. Barry Logan and M.J. Menendez are employees of NMS Labs.

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Death by Loperamide Overdose: Drug Abuse or Misuse?

JAMES L. CARUSO, MD

INTRODUCTION:

Loperamide (trade names Imodium, Diamode, Imotil, and others) is a synthetic opioid derivative that is used to decrease the frequency of bowel movements in patients with diarrhea. Once dispensed only by prescription, it has been available as an over-the-counter medication for over three decades. Loperamide was thought to have low abuse potential but there have been several fatalities due to this drug reported since 2015. Deaths attributed to loperamide are likely under-reported, as the scope of postmortem toxicological testing requested by the forensic pathologist would need to include this drug.

MAIN TEACHING POINTS:

1. Loperamide is a synthetic opioid that has opioid receptor agonist activity, similar to other opioids such as morphine. However, loperamide has some unique pharmacological characteristics that set it apart from the more mainstream opioids that are used for pain control.
2. Loperamide is frequently misused and death due to a loperamide overdose, while uncommon, has been recognized with increasing frequency during the past 8 to 10 years.

3. Loperamide causes death not through respiratory depression, which is the primary mechanism for most prescription and illicit opioids, but via its cardiotoxic properties.

Historical Perspective: Loperamide was first synthesized in 1969 by Paul Janssen in Belgium, who also created diphenoxylate and fentanyl. It first became available to the public by prescription in the mid-1970s. Clinical trials took place between 1972 and 1974 and full FDA approval was granted in 1976. It was promoted under the brand name, Imodium. At the time, both loperamide and diphenoxylate (trade name Lomotil) were used to treat noninfectious causes of diarrhea, such as inflammatory bowel disease and malabsorption syndromes. Lomotil is actually a combination of diphenoxylate, which is also a synthetic opioid, and atropine. Diphenoxylate was synthesized in the 1950s. While compounds containing diphenoxylate remain only available by prescription (US Schedule V), loperamide is widely available as an over-the-counter medication at nearly every pharmacy and grocery store. Loperamide and diphenoxylate both work by slowing intestinal contractility. Loperamide became the best-selling prescription drug for diarrhea during the 1980s.

Loperamide was originally classified as a narcotic and was initially placed on Schedule II of the Controlled Substance Act of 1970. It was subsequently moved to Schedule V in 1977, decontrolled in 1982, and in 1988, loperamide was designated an over-the-counter product.

Indications and Usage: Loperamide is widely used for short-term nonspecific diarrhea and gastroenteritis, as well as diarrhea caused by irritable bowel syndrome, short bowel syndrome, and inflammatory bowel disease. Loperamide is contraindicated for treatment of purely infectious diarrhea such as antibiotic-associated diarrhea caused by *Clostridium difficile*. Improper therapeutic use can result in complications such as toxic megacolon.

The side effects of loperamide include constipation, dizziness, nausea, abdominal pain, vomiting, drowsiness, and dry mouth. Rare severe side effects include paralytic ileus, anaphylaxis, angioedema, and Stevens-Johnson syndrome. It is also not recommended for very young children, as loperamide-related fatalities have been reported in children under three years of age, most of whom were malnourished and had dysentery. It is not recommended for use during pregnancy and breastfeeding due to limited clinical trials. There are numerous over-the-counter loperamide preparations marketed,

including caplets, oral dissolving tablets, chewable tablets, and a preparation in combination with simethicone. In 2013, loperamide was placed on the WHO Model List of Essential Medicines (2 mg tablet preparation).

Bioactivity and Bioavailability: Loperamide is a mu-opioid receptor agonist and has similar properties to morphine. Both morphine and loperamide have effects on the myenteric plexus of the large intestine that result in decreased bowel motility. Opioids decrease the tone of the longitudinal and circular smooth muscles of the intestinal wall, increasing transit time and decreasing the gastrocolic reflex. However, while morphine freely crosses the blood-brain barrier to depress central nervous system function, loperamide does not cross so freely because it is bound by P (for permeability)-glycoprotein (P-Gly) in the intestinal wall and circulation, limiting access to the central nervous system. P-Glycoprotein is an ATP-dependent pump in the cell membrane that actively transfers substances out of cells. While it likely evolved as a defense mechanism against harmful substances, P-Gly acts as a gatekeeper for many pharmaceuticals. Quinidine, a P-Gly inhibitor, if given concurrently with loperamide, allows the drug to cross the blood-brain barrier and produce typical opioid central nervous system (CNS) effects.

Loperamide undergoes extensive first-pass metabolism in the liver. It is metabolized into an MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-like compound that does not appear to be neurotoxic, unlike actual MPTP and MPP, which have been related to toxic effects on the cells in the substantia nigra ("chemical Parkinsonism").

In contrast, diphenoxylate, which is another local and centrally acting opioid drug used to treat diarrhea with similar indications as loperamide, has not been prone to abuse. Diphenoxylate was also synthesized by Janssen in 1956 and was created by combining a precursor of normethadone with norpethidine. It remains available by prescription only (Schedule V) and is available as a compound containing atropine to minimize the risk of abuse. Atropine blocks acetylcholine and causes nausea. Diphenoxylate is rapidly metabolized to difenoxin and primarily eliminated in feces and also in urine.

In summary, loperamide has limited bioavailability, undergoes extensive first-pass metabolism, and its bioactive effects are generally localized to the intestine. In order for significant CNS effects of loperamide to take place, a significant amount of the drug must be taken.

Abuse: Loperamide appears to provide some benefit in dampening the symptoms of opioid withdrawal; it has been called the "poor man's methadone." In very high doses, loperamide can provide some of the typical pleasurable effects of an opioid high. This is accomplished by achieving blood concentrations of loperamide sufficiently high enough to overcome the aforementioned obstacles to the drug's entry into the central nervous system. Central nervous system opioid receptors are stimulated, providing the typical response to opioids. The usual therapeutic dose is 2 to 6 mg; in abuse, the amount ingested may be 100-mg or even twice or three times that amount.

In the personal experience of this author as well in the cases of loperamide toxicity presented in the medical literature, excessive amounts of loperamide were being consumed for the express purpose of experiencing the pleasurable effects of opioid intoxication. In very rare cases the deleterious effects of loperamide may simply be a consequence of overmedication to treat symptoms of an actual illness.

Toxicity: The first reported death related to loperamide overdose occurred in 2015. There have been several reports of fatal loperamide overdose since then. How do excessive loperamide concentrations cause death? It would be convenient to say that the high blood concentrations simply overwhelm the defense mechanisms in place and result in a typical opioid-related overdose death via respiratory depression. It would also be incorrect.

While extremely high blood concentrations of loperamide will result in the drug crossing the blood-brain barrier, at very high concentrations loperamide appears to cause cardiac dysrhythmias/arrhythmia. The QT interval may be prolonged, and the QRS-interval may be widened. The end result can be ventricular dysrhythmias, with eventual cardiac arrhythmia and death.

Death Investigation: The investigation of a suspected death due to loperamide overdose, as with any suspected overdose, requires at least some suspicion of the drug or drugs involved. A standard medicolegal autopsy should be performed with toxicology testing that covers quantitative detection of loperamide. Because the mechanism of death may be cardiac rather than respiratory, some of the common signs of opioid overdose seen at autopsy may not be present. The scene investigation is critical and must be thorough enough to raise the suspicion that loperamide may be involved. Generally, in these cases, a history of opioid abuse or aggressive self-medication for gastrointestinal symptoms will be obtained from friends, family members,

or medical records. Evidence of purchasing large quantities of loperamide at local stores or through the mail may be present.

CASE 1: OVERTREATMENT OR RECREATIONAL?

History: A 27-year-old woman was found unresponsive in her residence by her live-in boyfriend (she had reportedly been on the couch watching television). Her medical history included endometriosis and severe pain from interstitial cystitis that was treated with an implanted sacral neurostimulator. She may have had a single seizure two years earlier associated with a fall.
The decedent complained of nausea and vomiting ("flu-like symptoms") throughout the day prior to her death and used over-the-counter medications to treat the symptoms. Her parents, who lived in another state, denied that there was any history of illicit drug use. However, a prescription in the decedent's name for Suboxone (buprenorphine/naloxone) was present in the residence. Resuscitation efforts were unsuccessful and death was pronounced at the scene.

Autopsy Findings: A complete medicolegal autopsy was performed approximately 10 to 11 hours after death. The body exhibited full rigor, with posterior livor that still slightly blanched. The decedent's BMI was 31.3 kg/m^2 and there was no evidence of trauma. The heart weighed 340 grams and the left ventricular wall had a normal thickness. Some froth was noted in the tracheal lumen. The lung weights were 480 grams on the right and 460 grams on the left, without evidence of significant pulmonary edema. The other organs were equally unremarkable. Histologic examination revealed mild pulmonary congestion and patchy chronic inflammation of the thyroid gland. There was no gross or microscopic evidence of endometriosis.

Histologic examination revealed mild pulmonary congestion and patchy chronic inflammation of the thyroid gland. There was no gross or microscopic evidence of endometriosis.

Laboratory/Ancillary:

Diphenhydramine 2000 ng/mL (typical therapeutic blood concentration up to 100 ng/mL)
Loperamide 630 ng/mL (typical therapeutic blood concentration up to 3 ng/mL)
Desmethylloperamide 3500 ng/mL (inactive)
Dextro/Levo Methorphan 160 ng/mL (therapeutic 2-4 ng/mL but can be 200 ng/mL in a poor metabolizer)

Dextrorphan/Levorphanol 17 ng/mL (therapeutic 8-20 ng/mL)
Caffeine and Naloxone - present
Vitreous Fluid analysis (electrolytes and glucose) was unremarkable
Nasal washings were positive for Influenza A virus by PCR
Postmortem blood cultures were negative for significant pathogens

Case 1 Conclusion: The case was signed out with the cause of death as "The Combined Toxic Effects of Loperamide, Diphenhydramine, and Dextromethorphan." Influenza A virus infection was noted as contributing to death. The manner of death was determined to be accident. There was no significant amount of loperamide found at the scene. The decedent had reportedly been taking Dramamine (diphenhydramine and 8-chlorotheophyline) "all day" for her symptoms, which explains the source of the diphenhydramine noted on toxicology. She was likely ill, perhaps with influenza, but most likely was using loperamide recreationally.

CASE 2: LOPERAMIDE WITH ANABOLIC STEROIDS

History: A 30-year-old man was found deceased in his residence by his roommates. His medical history included hypertension and headaches. His social history included remote cocaine use and cigarette smoking. No resuscitation efforts were attempted, and he was pronounced dead at the scene.

Autopsy Findings: A complete medicolegal autopsy was performed approximately 14 to 16 hours after death. The body exhibited full rigor, with posterior, fixed livor. The decedent's BMI was 24.1 kg/m^2 and there was no evidence of trauma. The heart weighed 470 grams and the left ventricular wall was slightly thickened. The other organs were equally unremarkable. Histologic examination was remarkable only for some myocyte hypertrophy, pulmonary congestion, and mild chronic portal inflammation.

Laboratory/Ancillary:
Trazodone 0.53 mcg/mL plus metabolite (low therapeutic range)
Loperamide 680 ng/mL (typical therapeutic blood concentration up to 3 ng/mL)
Desmethylloperamide 2400 ng/mL (inactive)
Caffeine and Cotinine - present
Urine was positive for Testosterone and Epitestosterone (ratio within normal range) and for Nandrolone (metabolite positive)
Vitreous Fluid analysis (electrolytes and glucose) was unremarkable

Case 2 Conclusion: The case was signed out with the cause of death as "The Toxic Effects of Loperamide". Anabolic steroid use and cardiomegaly were noted as contributing factors. The manner of death was determined to be accident. This was unlikely a case of loperamide overcompliance as it did not appear to have been used for therapeutic purposes. The decedent was noted to have been buying loperamide in bulk. There was no history of prior illicit opioid use.

CASE 3: BRUGADA SYNDROME AND LOPERAMIDE

History: A 45-year-old man arrived at a local airport on a flight and complained about feeling "weak and dizzy." He collapsed while riding in a vehicle with his son. Emergency medical services arrived and found his initial rhythm to be asystole. He was transported to a local hospital and pronounced dead shortly after arrival. The decedent had an automated implantable cardiac defibrillator (AICD) placed five years earlier for Brugada Syndrome. Other medical issues included obesity, anxiety, and complex migraines.

Brugada Syndrome is a genetic channelopathy (25% of cases can be associated with other family members). The most common gene involved is *SCN5A* (Na channel). The incidence of Brugada syndrome is 1-30/10,000; it is more common in males and more common in individuals of Asian descent. The signs and symptoms include dizziness, fainting, labored breathing (especially at night), palpitations, a fast and chaotic heartbeat, and occasionally seizures. Symptom onset is usually in adulthood and EKG findings may be inconsistently present. Treatment includes medical management vs. AICD placement.

Autopsy Findings: A complete medicolegal autopsy was performed approximately 24 hours after death. The body exhibited full rigor, with posterior, fixed livor. The decedent's BMI was 34.7 kg/m^2 and there was no evidence of trauma. The heart weighed 550 grams and the left ventricular wall thickness was at the high end of the normal range. There was an aberrant left coronary circulation, with a sharp downward angle taken by the left main coronary artery. There was also 20 to 40% luminal narrowing of the left coronary circulation by atherosclerosis. The right lung weighed 890 grams and the left lung weighed 750 grams.

Laboratory/Ancillary:

Nortriptyline 50 ng/mL (low therapeutic)
Citalopram/Escitalopram 74 ng/mL (low therapeutic)

Loperamide 960 ng/mL (typical therapeutic blood concentration up to 3 ng/mL)
Desmethylloperamide 2200 ng/mL (inactive)
Caffeine, Cotinine, and Naloxone - Present

Case 3 Conclusion: The case was signed out with the cause of death as a combination of natural disease (Brugada Syndrome, aberrant left coronary ostium, cardiomegaly) and the toxic effects of loperamide. The manner of death was determined to be accident. Additional history on why decedent's loperamide ingestion was so high was not available. Prior medical records were unavailable, and it would have been interesting to see if the diagnosis of Brugada Syndrome had been established by genetic testing. The toxic effects of loperamide mimic Brugada Syndrome. The implanted defibrillator was interrogated by the manufacturer and found to be functioning properly. The AICD reported two "non-sustained V oversensing" episodes on the morning of the decedent's death.

Loperamide Deaths in the Literature: Fatalities attributed to the toxic effects of loperamide were rarely reported before 2015. In one review of 26 nonfatal overdoses (2011-2016), 18 had known circumstances and included 12 misuse/abuse, three self-harm/suicide, and three accidental pediatric ingestions. The misuse circumstances included six avoiding withdrawal and four for pleasurable effects. In those abusing loperamide for pleasurable effects, the dosing ranged from 4 to 400 mg/day. For individuals avoiding withdrawal, dosing ranged from 160 to 400 mg/day.

In one case noted in the literature a 35-year-old man with a history of loperamide abuse was transported to the emergency department for altered mental status and frequent shocks from his AICD. The AICD had been placed six months earlier for prolonged QT syndrome. He had a history of intravenous drug use and previous loperamide overdoses. EMS personnel found a bag full of loperamide tablets near the patient at the scene. The administration of naloxone was ineffective, and the decedent experienced several more AICD shocks while in the emergency department. The patient was additionally diagnosed with electrolyte abnormalities and polymorphic ventricular tachycardia (torsades de pointes), but he survived this incident.

In another case reported in the literature a 48-year-old woman with a history of ethanol and benzodiazepine abuse presented to the emergency department with somnolence, slurred speech, and weakness. She had been taking 20

to 40 2-mg loperamide tablets one to two times per day for several weeks, along with clonazepam and whiskey. Her EKG demonstrated prolonged QT, prolonged QRS, and no P waves. The patient's blood ethanol was 70 mg/dL. Her loperamide concentration was 210 ng/mL and she had a large anion gap. She also experienced various cardiac dysrhythmias. After four days of treatment to correct her electrolyte abnormalities and dysrhythmias, the patient signed out against medical advice.

Death Certification: The Centers for Disease Control and Prevention and state health departments prefer that deaths attributed to the toxic effects of drugs are certified with all drugs that were felt to have contributed to the death listed in Part I of the Death Certificate (vs. simply using "Mixed Drug Intoxication" as the cause of death). This is essential for any meaningful epidemiological studies and research endeavors. In the vast majority of deaths attributed to loperamide, as is the case with most fatal overdoses, the most common manner of death is accident, with suicide being the second most common manner of death. If natural disease processes were felt to have contributed to a fatal drug intoxication, those conditions can be placed in Part II of the death certificate. Depending on how much the natural disease processes noted at autopsy were felt to contribute, the pathologist may choose to lead with them and include the drugs also in Part I or within Part II.

CONCLUSION:

1. Deaths due to the toxic effects of loperamide are uncommon but seem to be occurring more frequently in recent years.
2. Loperamide is available without a prescription, over-the-counter, and without restrictions regarding quantities or the age of the purchaser.
3. Despite being an opioid, loperamide's likely mechanism to cause death is cardiac dysrhythmia/arrhythmia.
4. If loperamide intoxication is a possibility, an appropriate toxicology panel must be requested.

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Fatal and Nonfatal NBOMe Intoxications: Novel Imported Designer Drug with Deaths and Intoxications in Multiple Jurisdictions

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INTRODUCTION:

A designer drug is a structural or functional analog of a controlled substance that has been synthesized to mimic and improve upon the pharmacologic effects of the original drug while hoping to avoid classification as an illegal substance and/or to avoid detection by standard drug testing procedures.

Designer drugs may have originally been synthesized by academic or industrial drug chemists to find more potent analogs of existing legitimate prescription drugs that would be more potent and have fewer side effects, potentially making the new drug eligible for a patent application. Designer drugs, as these drugs are more commonly thought of, are illicit drugs or are prescription drugs that are modified for recreational usage. These recreational drugs are manufactured classically in clandestine laboratories of varying degrees of sophistication. The Internet and social media give these drug labs and chemists instantaneous access to a worldwide marketplace for these "new and improved" products with the potential for extraordinary profits. Designer drugs are really not a new concept. In the early 1800s, morphine was derived from opium. In the late 1800s, heroin was synthesized from morphine. The 1960s saw the synthesis of hallucinogens such as LSD. Fentanyl was first

synthesized around 1960 and in 1968 was approved by the United States Federal Drug Administration for use in patients. The first illicitly synthesized fentanyl first appeared on the drug scene in the late 1970s and after that, a series of fentanyl analogs. MDMA (ecstasy) was synthesized and appeared as a club drug in the 1980s.

The laboratories that manufacturer these designer drugs vary considerably in their sophistication and consequently there are multiple unknows associated with designer drugs. There are inconsistencies in production that lead to considerable variation in potency and purity. Contaminants may be present in the final product as a consequence of the manufacturing process or by intentionally introducing "cutting" agents. These drugs have no legitimate use in humans and have undergone no clinical trials. These designer drugs may have inconsistent and/or unknown harmful effects on the users. Finally, there may be false, misleading, or deceptive sales practices in the marketing of these products.

MAIN TEACHING POINTS:

1. Synthetic "designer drugs" pose a significant challenge for medical examiners.
2. The identification of novel drugs that result in death requires diligence in investigating sudden deaths.
3. Collaboration with local hospitals and law enforcement is an essential component of the investigation.

Case Reports: In 2012, a new drug arrived in the northern part of the Red River Valley along the border of North Dakota and Minnesota. Over a two-week period, there were two deaths, one hospitalization, and three emergency room visits attributed to a new designer drug. The first series of five intoxications (Cases 1-5) were from one incident that occurred in a residential neighborhood of North Dakota. The second incident (Case 6) involved a single death.

Case 1. The Medical Examiner was called to a scene of death of an 18-year-old male found lying prone on a sidewalk in a residential neighborhood and who was reportedly "beaten to death." Examination of the injuries showed extensive but superficial terminal fall-type abrasions, primarily of the face and chest. Overall, the injuries gave the appearance that the individual collapsed and died suddenly, perhaps while running. He was reported to have ingested a drug at a nearby party in a private residence. An autopsy examination

showed a well-developed and well- nourished young adult male (body height 75.5 inches tall and weighing 263 pounds). External examination showed the superficial terminal fall abrasions described above. Internal examination showed pulmonary congestion and edema (lung weights 760 grams [right] and 660 grams [left] with pink frothy foam in the upper airways along with mild cerebral edema. There was no other evidence of other injury or natural disease.

Case 2. A second individual, a 15-year-old male, was found nearby acting bizarrely. He was taken into police custody with some difficulty as he was highly combative and violent. Law enforcement was initially going to transfer the young man to jail; however, as he was so difficult to control, the decision was made to take him to the local hospital for evaluation. In the emergency department, the physician in his notes described the patient to be in an "excited delirium" and that he "required 8-10 people to hold him to the gurney."

Attempts at sedation with haloperidol and lorazepam were unsuccessful as he "became more agitated". Due to his extreme agitation, it was decided to more heavily sedate, paralyze, and intubate the patient and move him to the intensive care unit for close observation. A urine drug screen was positive only for cannabinoids. A computed tomography (CT) scan of the head was negative. Significant laboratory findings were a creatinine phosphokinase of 629 U/L (normal: 39-308 U/L), which later peaked at 1435 U/L before normalizing, and a serum potassium of 3.1 mEq/L (normal: 3.6-5.5 mEq/L). Supportive care was provided and the patient was extubated 24 hours after admission and then discharged two days later without apparent sequalae.

Case 3. An 18-year-old male was found wandering naked in a nearby park. He was initially uncooperative but was easily controlled and had only a very minor foot injury. Laboratory findings showed only a mild elevation of creatinine phosphokinase. A urine drug screen was negative. The young man stated that he took "some LSD". He was treated with intravenous fluids, observed, and then released several hours after admission to the emergency department.

Cases 4 & 5. Two other teenagers were involved and admitted that they ingested the drug and reported only a very hallucinogenic response. Drug screens on both individuals were negative. There were no deleterious consequences associated with the drug intake. These young men were

observed in the hospital emergency department for several hours and then released.

At the residence where these individuals ingested the drug, a small plastic bag was recovered, which contained a white powder. Qualitative testing at the North Dakota State Toxicology Laboratory identified by mass spectrometry a derivative of the substituted phenethylamine 2C-I family of drugs, the most common of which is 25I-NBOME.

Case 6 (One week later). A 17-year-old male was at home in Minnesota, near the North Dakota border. He was lying on a couch and told friends and family that he wasn't feeling well as he had done some "bad mushrooms." Friends would check on him periodically. He was eventually found unresponsive and not breathing. Resuscitation by emergency responders was successful; however, after hospital admission he remained comatose and required mechanical ventilation. A urine drug screen on hospital admission was negative. A CT scan of the head was negative. Over the course of the next 48 hours, his condition deteriorated and he was pronounced dead. Autopsy examination showed a well-developed, wel-nourished male who was 68 inches tall and 125 pounds with no evidence of injury. Internal examination showed only cerebral edema (brain weight: 1680 grams) and a mild and focal, aspiration bronchopneumonia. Initial investigation linked this death to the previous series of drug intoxications. This individual was an acquaintance of the young men associated with the first series of intoxications and from one of them he was believed to have obtained a small sample of the drug.

Toxicology: NBOMe drugs are potent serotonin agonists and produce the so called "serotonin syndrome." Anecdotal reports suggest that these drugs may be active hallucinogens as insufflated doses of as little as 200-500 micrograms. Medical treatment is supportive. Reported laboratory findings include metabolic and respiratory acidosis, an elevated white blood cell count, elevation in creatinine phosphokinase due to rhabdomyolysis, and impaired renal function, with a negative routine toxicology screen.

Fatal Cases 1 and 6: Analysis of specimens collected at autopsy and upon hospital admission were analyzed by liquid chromatography with tandem mass spectrometry.

Case 1:	25I-NBOMe	2.7 ng/ml
	25C-NBOMe	7.2 ng/ml
Case 6:	25I-NBOMe	2.1 ng/ml

25I- and 25C- metabolites were detected in both fatal cases.

Nonfatal Cases 1, 2, 3, 4 & 5: 25I-NBOMe, 25C-NBOMe: None Detected Positive for 25I- Metabolites

Death Certifications:
Case 1: Cause of Death: Acute drug toxicity (25I-NBOMe, 25C-NBOMe); Manner of Death: Accident

Case 6: Cause of Death: Anoxic Encephalopathy as a Delayed Complication of a Drug Toxicity (25I-NBOMe); Manner of Death: Accident

NBOMe Drugs: NBOMe drugs are a series of substances that are derivative of β-phenylethylamine (25I-NBOMe, 25C-NBOMe and 25B-NBOMe). They are collectively known as "2C" drugs, as two carbon atoms separate the amine from the phenyl ring. These compounds contain a methoxy group in positions 2 and 5 and a hydrophobic 4-substituent (Iodine in 25I-NBOMe and Bromine in 25B-NBOMe). Street names include N-Bomb, Boom, 25I, 25C and 25B. This drug can be found as a liquid, powders, in edibles, and on blotter paper. These drugs are known for their potent hallucinogenic effects and NBOMe drugs on blotter paper are commonly sold as LSD. Side effects include severe agitation, erratic behavior, anxiety, paranoia, and psychosis. Seizures along with cardiac and respiratory arrest have been described. NBOMe drugs were first synthesized by Alexander Shulgin in the 1970s and 1980s. Descriptions of the effects of these drugs were reported by Shulgin and on the Internet. Internet references to these drugs began around 2011. There are no known legitimate uses for the drugs and consequently there have been no clinical trials. 25I-NBOMe has been reported to the most commonly encountered version of the drug. There appears to be no difference in the effects between the different NBOMe Drugs. The most common route of administration is the oral/sublingual route via blotter paper. These intoxications reported show a spectrum of complications ranging from mild euphoria to acute psychosis to sudden death. An investigation by a multiagency task force determined that the drugs in these cases were ordered on the Internet and imported from a supplier in China.

Problems Encountered and Lessons Learned:
The first problem was obtaining specimens for toxicological analysis. Case 1 did not present such problems, as suitable specimens were obtained at autopsy. In Case 6, the death was delayed, occurring more than two days after admission and very little admission blood, serum or urine were available for testing. Likewise, in Cases 2, 3, 4 and 5, very little blood, serum, or urine was available for testing.

The United State District Attorney along with local and federal drug task forces opened an investigation into the deaths and intoxications. Our medical examiner's Office acted as a clearing house for collecting and submitting specimens for toxicological analysis, for both the fatal cases as well as the cases in which the individuals survived their suspected drug encounter. Hospitals have limited storage for clinical specimens. In delayed drug deaths or intoxications, the patients are largely treated symptomatically and often collect little in the way of specimens (blood, urine, serum) for laboratory testing and discard these specimens after a time prescribed by laboratory policy. We were able, with some effort, to locate a minimal quantity of suitable specimens to submit for toxicological analysis. The local hospital has a large coverage area that closely matches the jurisdiction of our medical examiner's office.

Our medical examiner's office representatives met with the emergency department nursing service and described our problem. The hospital instituted a policy that if someone is admitted to the hospital due to a suspected drug toxicity, admission blood would be obtained (multiple fluoride-containing tubes) and held for toxicology (stored in a separate area so as not to be discarded). Also, it was decided to develop an ongoing dialog with the emergency department and the hospital so all involved could be aware of shifting trends in the type of drugs being seen in hospital emergency departments and the medical examiner's office.

Developing relationships with local and regional law enforcement agencies is crucial in investigating potential drug deaths with novel designer drugs. This is highlighted by the fact that each of the individuals described in our series of death and intoxications had an initial negative toxicology screen at the hospital. Without the report that an NBOMe drug had been identified from the party scene from which one of the deaths and the four intoxications arose, the identification of the novel designer drug responsible in specimens obtained from the participants may not have occurred.

This also extends to dealing with the toxicology laboratories utilized by the medical examiner's office. Relaying the information that a novel designer drug may be present in the samples submitted is critical. As novel designer drugs find their way into the drug using culture, there may be some lead time necessary for toxicology laboratories to develop methods and procedures to test for and quantitate these drugs in biological specimens. This may also influence the decision to use a particular toxicology laboratory.

In investigating suspected drug intoxications and sudden and unexpected deaths in which the initial screening toxicology testing is negative, the possibility that a novel designer drug is responsible must be considered. The collection of adequate specimens for testing is paramount, particularly the obtaining of hospital admission specimens in delayed deaths. This may require an ongoing dialog between law enforcement drug task forces, hospital staff, and the medical examiner's offices to identify possible drug associated deaths and take the necessary steps to procure adequate biological specimens for testing.

FURTHER READING:

EROWID is a website (https://www.erowid.org) that is a considerable resource when investigating novel drugs. EROWID is listed as a nonprofit educational & harm-reduction resource with sixty-thousand pages of online information about psychoactive drugs, plants, chemical and technologies.

Additional peer-reviewed information regarding NBOMes published by researchers, practitioners, and academicians is available at PubMed.com and CFSRE's NPSDiscovery.org.

CHAPTER TEN

Forensic Toxicology Mistakes by the Forensic Pathologist

JAMES R. GILL, MD AND CANDACE H. SCHOPPE, MD

INTRODUCTION: Alexander Gettler is considered by many to be the grandfather of forensic toxicology in the United States.[1-3] Alongside Charles Norris, the first appointed chief medical examiner in New York City, Gettler became one of the first forensic chemists in the United States. Together, they laid the foundation for what we now consider standard practice in forensic pathology and medicolegal death investigation. Gettler's research on various drugs, toxins, and poisons (used intentionally and accidentally) established ground truths that we now take for granted, including our understanding of carbon monoxide intoxication.[4]

Gettler did not gain his knowledge secondhand; much of what we know and how we use forensic toxicology today was developed via trial and error to answer new, and sometimes unfathomable, questions as to how and why someone died.[5] The organic development of forensic chemistry alongside the modernization of forensic pathology and the death investigation system in America afforded the notion that mistakes are inevitable and only by continual questioning, consistent and thorough collection of information, and collaboration between the forensic chemist/toxicologist and the well-informed forensic pathologist can these "mistakes" be recognized.

"If you don't make mistakes, you're not working on hard enough problems. And that's a big mistake." -Frank Wilzcek

Charles Hirsch, a modern successor of Norris, led the New York City Office of Chief Medical Examiner from 1989 until 2013, which still includes the toxicology division. The late Charles Hirsh was known to say that "he was glad his job description didn't contain the adjective, 'infallible'." Despite the best and most conscientious efforts, mistakes are inevitable. As impartial participants in the criminal justice system, we must willingly recognize and correct any errors or mistakes. The life and liberty of real people depend upon the integrity of our work, which includes the maturity and willingness to accept that we cannot and will not be perfect every time.

"Smart people learn from their mistakes. But the real sharp ones learn from the mistakes of others" -Brandon Mull

In 1956, Alan Moritz gave a lecture at the annual meeting of the American Society of Clinical Pathologists on "Classical Mistakes in Forensic Pathology."[6] He included a small section on toxicology mistakes. Toxicology testing is an integral part of forensic pathology practice.[7] Improper testing or ill-considered/impulsive interpretation may lead to an incorrect diagnosis with disastrous consequences, such as mislabeling a death a suicide or failing to detect a homicidal poisoning. It is becoming increasingly common for accidental drug deaths to lead to criminal charges against the drug supplier, even though the supplier had no role in the administration of the drug.[8] Therefore, families, the accused, law enforcement agents, attorneys, public health officials, and other stakeholders need reliable and, at least jurisdictionally consistent determinations in drug-related deaths.

THOUGHT PROVOKING QUESTIONS:

- What to consider when interpreting a drug concentration?
- Why are the circumstances and the autopsy findings essential to consider in a fatal intoxication?
- What information should be shared with the forensic toxicologist?
- When does the intoxication belong on the death certificate?
- What can be said (or not said) when testifying in court on a death that involves an intoxication?

MAIN TEACHING POINTS:

Toxicology results must be considered in the context of the circumstances and the autopsy findings. In current usage, the word "intoxication" has replaced

"poisoning," which has a more sinister connotation. Since most deaths due to an intoxication are primarily a diagnosis of exclusion, one needs all the information to certify the death correctly. Three components must be considered when diagnosing a fatal drug intoxication:[9]

1. The autopsy fails to disclose a disease or physical injury whose extent or severity is inconsistent with continued life.
2. The toxicology results are in the range typically encountered in such deaths.
3. The history and circumstances are consistent with a fatal intoxication.

Did a person die from a substance or just die with a substance? Toxicology results belong on the death certificate when they make a physiologic contribution to death or when the circumstances do not make sense without them (e.g., positional asphyxia, adult choking on a bolus of food, or a healthy adult accidently drowning in a bathtub).

When multiple drugs are detected, it may be impossible to tease out each drug's role in the cause of death. Recommendations set forth by the Centers for Disease Control and Prevention (CDC) and the National Association of Medical Examiners (NAME) agree that the cause of death statement should include all of the drugs (usually with concentrations greater than trace amounts) that make a physiologic contribution to death.10 Therefore, a death with fentanyl, methadone, heroin, and alprazolam would have all four intoxicants listed in the cause of death. There are synergistic effects that should not be ignored. Drug concentrations, per se, usually are not determinative of the cause of death. Toxicological data are no substitute for an entire death investigation and the exercise of medical judgment to evaluate these deaths. Tolerance and other variables result in a wide range of drug concentrations causing death, particularly with chronically used (e.g., methadone) and misused (e.g., heroin) substances. Analytical tests do not speak to tolerance. The toxicology laboratory may provide an accurate postmortem concentration, but does it accurately reflect the premortem concentration or the concentration at which that substance will be fatal to that individual?

When considering such variables, communication with the toxicology laboratory is vital. The more information provided, the better will be the scope of testing. No laboratory can test for every drug/chemical as part of routine testing and each laboratory has their own scope of testing and panels.

Communication also extends to the National Center for Health Statistics, law enforcement agents, attorneys, and families.

There are several areas in which mistakes can be made in an investigation of a suspected drug intoxication death.6, 11 These include mistakes involving the: investigation, toxicological analysis, interpretation of results, death certification, and testimony in court. These mistakes involve failure to consider the circumstances and variations in postmortem concentrations; perform an autopsy if indicated; communicate fully with the forensic toxicologist; properly certify a death; properly testify, and observe practices that ensure personnel safety.6, 11-13

Investigation Mistakes

Scene: Experience has shown that some law enforcement agents may not be as aware of the subtle signs of substance use at death scenes as trained medicolegal death investigators. The need for a scene investigation by a medicolegal death investigator should not be underestimated.[14] The initial triage of the report of any death is a critical component of death investigation.

Once jurisdiction is declined, it is rare to get a second opportunity to reconsider. Improper triage and inadequate scene investigations can miss drug intoxication deaths. Examination of medical records (prior hospitalizations) and access to prescription drug monitoring sites may provide further objective information about substance use. One should not rely solely on the presence or absence of drug paraphernalia at the scene to make a determination.

A study by Lozano *et al.* examined the detection of drug paraphernalia at death scenes. They found that 80% of fatalities with drug paraphernalia at the scene were drug intoxication deaths (20% were not). And only 24% of drug intoxication deaths had paraphernalia at the scene.[15] One must not fail to do pill counts because possible suicides may be identified from the later toxicology results.[16] A photograph of the pill container and the remaining pills poured out on a table will suffice.

Admission Hospital Sample: Failure to obtain an admission sample of a delayed intoxication or traumatic death (e.g., homicides, intoxications, motor vehicle collisions) may hinder an investigation. Investigators are concerned with the intoxication state at the time of the injury, not what is detected at autopsy after a two-day survival interval. If the chemistry or hematology lab has already discarded the specimen, one should check with the blood bank

because most trauma admissions get a type and cross specimen and the blood bank usually retains it for at least seven days. In addition, hospital therapy including massive blood transfusion protocols/fluid resuscitations may affect concentrations of later samples.[13, 17]

Safety: Investigators and autopsy personnel must be aware of unexpected or unanticipated hazards that may result in infectious and chemical exposures. Universal precautions must be followed.[18] Investigators and autopsy personnel should take care with checking pockets to avoid an accidental needle stick or other sharp injury There are also homemade suicide chemical mixtures that produce noxious gases (carbon monoxide, hydrogen sulfide). A call to a HAZMAT team is appropriate in these scenarios.[19-24]

Autopsy: According to the current National Association of Medical Examiner's (NAME) forensic autopsy standards, autopsies should be performed in suspected drug intoxication deaths that have not been hospitalized.[7] Failure to perform autopsies in these deaths will miss disease or trauma-related causes of death that supersede the intoxication. Without an autopsy, the cause of death in suspected drug-related deaths may be incorrect in approximately 10-20% of instances.[25, 26]

Documenting the volume of the gastric contents is needed to determine the amount of drug in the stomach. An elevated concentration of drug may help demonstrate the intent required for a suicide determination. However, a low drug concentration in the stomach does not exclude a significant ingestion of drug. Aside from delayed-release drugs, most drugs are meant to dissolve rapidly in the stomach and be absorbed in the gastrointestinal tract. Thus, the gross detection of pills or pill fragments is infrequent. Given a potential survival interval, much of the ingested drug may be absorbed or moved into the small intestine by the time of death.

Communication: Failure to provide the forensic toxicologist with information about the circumstances deprives a key player in this investigation of information that may help the forensic pathologist. Neither the testing nor the interpretation of toxicology results should be made in a vacuum. Both teams need to be aware of the scope of testing and when additional testing may be required. Having two sets of eyes looking at this is best. Depending upon the laboratory, substances that may not be included in the routine scope of testing include ethylene/propylene glycol, carbon monoxide (methylene chloride, suicide mixture), cyanide, heavy metals, nitrites

(methemoglobinemia), vitreous analysis (glucose/electrolytes), fentanyl and benzodiazepine analogues, and other novel psychoactive substances (NPS). One may keep a list of included drugs handy to confirm their inclusion in the scope of testing.

Toxicological Analysis Mistakes

False positives and false negatives do occur but are not covered by this review. For example, there may be false positives for amphetamine (e.g., ephedrine, metoprolol), issues with distinguishing enantiomers, or the amphetamine may be a metabolite from a prescribed medication (e.g., Selegiline).[13, 27-31]

Interpretation Mistakes

Interpretation mistakes may occur when not considering the circumstances and autopsy findings. The toxicology report gives us data, but not conclusions. Therefore, one must take care when interpreting drug concentrations with respect to the cause of death. Other factors influencing or affecting drug concentrations include the survival interval, decomposition, sample collection (e.g., site and time) and storage, postmortem drug redistribution, tolerance, and underlying disease.

Many textbooks discuss the "fatal" concentration. It is generally best to avoid this dogmatic approach to forensic toxicology interpretation. In persons who are dead, what constitutes a fatal concertation? Is it the minimum concentration that always causes death? Or is it the minimum concentration that typically causes death? Or is it the minimum concentration known to cause death? Some deaths are clearly due to excessive drug (an acute overdose); however, the forensic pathologist will undoubtedly encounter toxicology results in individuals who clearly did not overdose but have far greater concentrations than those who have overdosed.

Regardless of the toxicology results, the prudent forensic pathologist will consider whether a person died from a drug or simply with the drug. Common reasons for the ambiguity regarding fatal drug concentrations include change in potency, change in drug, polysubstance use, lack of a medical response (e.g., naloxone administration), comorbidities, and route of administration.

Less common but nonetheless important factors to consider include adverse drug reactions that are not necessarily concentration dependent, such as allergic and idiosyncratic reactions, side effects, intolerance, genetic variations, and interactions with other drugs, medications (including over the counter

medications), herbal and other holistic supplements, and even certain foods (e.g., grapefruit juice).[32]

Baselt's *Disposition of Toxic Drugs and Chemicals in Man* is an invaluable compendium of hundreds of common drugs and chemicals.[33] It offers a summary of studies that provide various drug concentration ranges in deaths and in living/surviving individuals. But these drug concentration ranges should not be taken as an absolute answer. The quoted studies give ranges in cohorts of deaths that include heterogeneous populations, which may not be entirely representative of the population under query.

Many factors affect postmortem drug concentrations that may not be clear from summary statistics. As a simple example, in a given cohort, was the tested sample from central or peripheral blood? Were there other intoxicants? Was there a survival interval? Did tolerance or underlying disease a play a role? Did that disease increase the decedent's risk of death, or did it arise as a consequence of the initial intoxication, such as bronchopneumonia?[34]

The reported fentanyl concentrations in fatal cases show a range of 2.2-383 μg/L.[33] There are well-documented instances of deaths due to fentanyl with postmortem concentrations below 2.2 μg/L, and there are well-documented instances of fentanyl concentrations of over 200 μg/L in live persons, including one of 303 μg/L (e.g., driving under the influence).[35, 36]

Concerning postmortem drug concentration, factors that must be considered include redistribution, drug-protein binding changes, postmortem clotting of blood (e.g., syringe), postmortem dehydration (i.e., decomposition), postmortem metabolism (e.g., cocaine), and postmortem "production" (e.g., ethanol).

Postmortem Redistribution: Postmortem redistribution (PMR) refers to variations in drug concentrations after death.[37] This redistribution to blood occurs from solid organs such as the lungs, liver, and myocardium. The drug's volume of distribution, lipophilicity, and pKa are important factors with regard to the extent of PMR. For example, basic, highly lipophilic drugs with a volume of distribution greater than 3 L/kg are more likely to undergo PMR. The volume of distribution is a measurement of a drug's tendency to undergo postmortem redistribution expressed in liters per kilogram of body weight. It represents the apparent volume into which the drug is distributed to provide the same concentration as it currently is in blood plasma. It is calculated by

the amount of the drug in the body divided by the plasma concentration. The volume of distribution is the theoretical volume necessary to contain the total amount of an administered drug at the same concentration that it is observed in the blood plasma.

Common drugs that undergo PMR include tricyclic antidepressants, digoxin, and amphetamines. The site of the blood sample can influence the drug concentration. A peripheral site (e.g., femoral vein) is preferred to minimize the amount of PMR (femoral blood, however, does not equate with antemortem blood concentrations). PMR must be considered when interpreting postmortem drug concentrations and correlated with clinical and autopsy information for proper death certification.

Postmortem Sample Collection: Location and Postmortem Interval: A study by Crandall et al. tested morphine concentrations in 76 decedents from a variety of sites at autopsy (femoral artery and vein, left and right ventricle, and pooled heart blood). They found that both free and total morphine values show marked variation among sites within the same person.[38] A study by Andresen et al. compared postmortem femoral blood concentrations from 118 decedents with therapeutic use of fentanyl to serum concentrations of 27 living patients with therapeutic fentanyl patches. They reported that postmortem fentanyl blood concentrations averaged up to nine times higher than in vivo serum at the same dose.[39]

A study by Olson *et al.* demonstrated that postmortem fentanyl concentrations increased with increasing postmortem interval, even in femoral blood. Postmortem femoral blood was collected from seven decedents at two postmortem intervals with mean collection times of 4.0 and 21.6 hours, respectively. The fentanyl concentrations ranged from undetectable to 14.6 μg/L (mean, 4.6 μg/L) and from 2.0 to 52.5 μg/L (mean, 17.3 μg/L), respectively.[40] Postmortem blood is not homogeneous and may have clots and separation of blood components. For example, collecting blood with a syringe may collect the "liquid" component and not the clot that remains in the vessel.

Decomposition causes the body to dehydrate; fluids will shift, which will affect drug concentrations. Decomposition fluid often pools in the pleural cavities and may be collected for testing in these instances. In decomposed remains, one should be hesitant to use the drug concentrations to drive cause or manner of death determinations.

Postmortem Production and Metabolism: Due to endogenous bacterial fermentation, postmortem ethanol production may produce blood concentrations of over 0.2 gm%, although most are below 0.1 gm%.[41] Cocaine undergoes postmortem hydrolysis and plasma containing cocaine stored at 20ºC loses nearly 100% of its original content after one day without a preservative (e.g., NaF).[42]

Hospital Toxicology and Specimen: It is a mistake to fail to recognize the difference between hospital toxicology testing and forensic testing. Except for ethanol testing, most substance use testing at hospitals involves a rapid urine drug screen test without a confirmatory test. This does not meet forensic standards. The scope of testing is often limited (some may not include fentanyl) or will only detect classes of drugs (e.g., benzodiazepines). Detection of "cocaine" on a typical urine drug screen is actually detecting benzoylecgonine (BE).

Specimen Type, Units, and Terminology: The specimen that was tested (e.g., whole blood vs. serum/plasma) will affect the concentration. One would need to convert the serum/plasma ethanol concentration to a whole blood concentration (divide by 1.2-1.3). The legal standard for ethanol intoxication is the concentration in whole blood. Hospitals also may report ethanol as mg/dL (0.1 gm% = 100 mg/dL). In scientific and medical writings, the word "concentration" is preferred to "levels." Regarding terminology issues, there is a difference between a corrosive and an irritant. An irritant (e.g., chlorine gas, poison ivy) causes an inflammatory process that does not occur after death. A corrosive is a chemical agent that will dissolve/damage the body. The corrosive action may continue after death.

Specimen Collection Tube: Failure to recognize the blood tube collection type (different colored tubes have different additives) used to collect antemortem blood, or to select the appropriate tube for postmortem collection may lead to confusion in the interpretation of results. A gray top tube (containing sodium fluoride as a preservative) is generally best for forensic drug testing as it prevents postmortem production of ethanol, clotting, and cocaine from spontaneously hydrolyzing. In general, one would like to detect cocaine in the blood to certify a death as an acute cocaine intoxication.[43] There are instances when an acute cocaine intoxication may be used to certify a death with only benzoylecgonine (BE), and no cocaine detected in the blood.[44] An example would be a decomposed, otherwise healthy, 22-year-old man found with a crack pipe and lighter in his hands. There is a reasonable explanation

why cocaine was not detected (postmortem breakdown), so this death may be certified as an acute cocaine intoxication. In more equivocal cases, one may include "recent cocaine use" usually in part 2 of the death certificate.

Incorrect choice of specific blood tube types or storage, may cause other issues. For example, GHB may be artificially elevated in citrate-buffered blood samples.[45] A green top tube is recommended for CO saturation testing. Exposure of serum containing clonazepam to sunlight can cause up to 99% loss of the drug within one hour.[46]

Death Certification Mistakes

The degree of certainty for a cause of death correlates with the extent and severity of objective autopsy findings in conjunction with scene findings and investigative information; most are more comfortable certifying a death due to multiple gunshot wounds than a subtle homicidal strangulation. Although toxicological analysis provides reliable, objective data, these concentrations must not be taken as gospel (see above). It may be an accurate postmortem concentration, but does it accurately reflect the concentration just before death? One needs to look at the whole picture when investigating deaths due to intoxication.

Inappropriate inclusion on the death certificate: Just because an illicit drug is detected at autopsy does not mean that the result must be included on the death certificate. Intoxications are included on the death certificate in two situations. The first is when the intoxication makes a physiologic contribution to death; the second is when the circumstances do not make sense without it. In most instances, toxicology results should not be listed as the cause of death in an attempt to explain why a traumatic death occurred (e.g., crashing a car while under the influence of ethanol). The forensic pathologist did not autopsy the car. Families and attorneys often will look for "why" the injury happened. Why it happened usually does not translate to the cause of death.

Exceptions to this rule include deaths due to positional asphyxia, an adult accidently drowning in a bathtub, or an otherwise neurologically intact adult choking on a bolus of food. The intoxications in these deaths are the proximate cause. A person who dies of a gunshot wound (GSW) of the head may have been under the influence of alcohol but died of the GSW. The alcohol played no physiologic role in the death, and the GSW would have caused death regardless of the intoxication. If a violent cause of death can stand alone on the death certificate without a contributory condition, it should do so.

Some medical examiners/coroners may include drug intoxications in all trauma deaths, even if they did not play a role in the death. One reason given is for public health surveillance data to know, for example, how many motor vehicle collision drivers or homicide victims were intoxicated. These diagnoses are often listed in part 2 of the death certificate. Listing these in part 2 defies the rule for what belongs in part 2. Per instructions set forth by the CDC/NCHS for completing part 2, it is for "other significant conditions contributing to death but not resulting in the underlying cause given in part 1." If a researcher wants to know the intoxication rate of homicide victims, they should review the autopsy and medical records and not rely solely on the death certificate. Variations in practice and delayed deaths in which toxicology was not done will skew intoxication data based on death certificates and lead to unintended consequences in homicide adjudications (e.g., contributing the use of cocaine to explain the fatal homicidal gunshot wound).

Inconsistency with Complex Cause of Death: The inclusion of intoxications in restraint deaths is reviewed in this compendium of presentations. In restraint deaths, the certification depends upon how confident the certifier is that the death is due solely to a single fatal injury (e.g., choke hold). For example, there is no need to invoke contributing conditions in a typical suicidal hanging. Restraint deaths may involve an asphyxial component with minimal supporting autopsy findings. In deaths with equivocal fatal injury infliction, one may consider a stress/homicide-by-heart attack scenario in which it is appropriate to include factors that reasonably contributed.[47-49]

For example, intermittent applications of neck/chest compression or prolonged durations of conscious struggle that do not fit with the time course of the pathophysiology of neck compression may implicate the use of part 2 contributing conditions.[50, 51] The forensic pathologist must avoid falling into the fallacious "either/or" approach. As Adelson noted, *"No mutually excluding entities exist here. Rather, one may be dealing with a conglomeration of several different harmful processes, each capable of aggravating and enhancing the deleterious effect of the others."*[52]

Not certifying the death as an accident: The NAME opioid position paper recommends classifying deaths from the misuse of opioids without any apparent intent to do self-harm, as accidents. In these instances, assigning "undetermined" as the manner of death as a matter of course does not serve the public good, nor does it support efforts to intervene and prevent future intoxication deaths.[10, 53, 54]

Not listing the specific drugs: For a natural or accidental cause of death, the degree of certainty needed for certification is a probability. One is never required to be 100% certain for any cause or manner of death, including homicides. By extension, this includes the involved substances. Usually, one cannot tease out the individual drug roles, and so all with a similar or contributing mechanism of death are invoked. Public health investigators only have access to the death certificate, so it should be as comprehensive as possible while still following the certification guidelines.

Public health education efforts have increased the specificity on death certificates. Terms such as "multidrug intoxication" are insufficient. Instead, one should use: "multidrug toxicity including…" or "acute intoxication due to the combined effects of…"[53-57] This degree of certainty becomes an issue with some heroin deaths.

Heroin vs. Morphine: Heroin is rarely detected at autopsy because it is essentially a prodrug that is rapidly converted to 6-monoacetylmorphine (6-MAM). The 6-MAM has a half-life of minutes and is converted to morphine which has a half-life of about 2 hours. Therefore, morphine is invariably detected in heroin deaths. As 6-MAM is a unique metabolite of heroin, its detection conclusively diagnoses the use of heroin. Without the 6-MAM, some forensic pathologists are reluctant to put "heroin" on the death certificate and instead use "morphine."

This "heroin-morphine" dogmatism hinders the collection of public health information. The argument for using morphine instead of heroin is that since only morphine was detected, one cannot be 100% certain that the result is due to morphine versus heroin use. As discussed above, the degree of certainty needed for an accidental drug intoxication is a probability. The detection of a syringe and drug packets at a scene should be considered in the certification of a death in which only morphine is detected. In the absence of 6-MAM, if there is toxicological and circumstantial evidence that allows a reasonable conclusion that a death is due to heroin, then the death may be certified as due to heroin. A forensic pathologist does not need to be 100% certain that the used drug was heroin. For example, a small amount of codeine may be detected with morphine in heroin deaths. Codeine may be detected with heroin (and has been rarely detected with morphine[58]) as an impurity due to the processing of opium, which also contains codeine.[58-65] Some codeine is normally metabolized to morphine but morphine is not metabolized to codeine. Therefore, a high ratio of morphine to codeine supports heroin use.

In contrast, higher concentrations of codeine, compared to morphine, favor the independent consumption of codeine. When a small amount of codeine is detected with a larger concentration of morphine and other findings support illicit drug use, such as the presence of cocaine in the same sample, autopsy findings indicative of substance misuse (i.e., "track marks"), and/or drug paraphernalia such as drug packets, syringes, or spoons at the scene, it is more likely than not, based on that information, that the detected morphine is from heroin. One should not deny reality for the sake of objectivity.

A study by Harruff *et al.* examined the tracking of the opioid crisis in King County, Washington.[65] The study's outcome resulted in developing a protocol to better track heroin deaths in the absence of the detection of 6-MAM based on the scene investigation and the toxicology results. As Rick Sanchez said, "Sometimes science is more art than science."

Isopropanol: Isopropanol can be produced with putrefaction or may be seen in deaths with ketoacidosis. Acetone and isopropanol can be in chemical equilibrium. Without other compelling information, one should not diagnose an isopropanol intoxication in these instances. β-hydroxybutyrate and the ratio of acetone to isopropanol may further help to distinguish the endogenous vs. exogenous nature of the isopropanol.[66-75] The detection of acetone, particularly in a non-decomposed body, should lead to vitreous glucose testing to investigate diabetic ketoacidosis.[76-84]

Testimony Mistakes

At trial, there are common toxicological questions posed to a variety of experts including forensic toxicologists, medical toxicologists, emergency medicine physicians, and forensic pathologists. During their careers, forensic pathologists will be asked time and again, when testifying on cases unrelated to toxicological causes of death: Did this drug contribute to death? Or did this drug make the person belligerent, aggressive, etc.? We can describe common effects of drugs but cannot predict in a particular person how they will specifically react to drug X at concentration Y.

For example, would a cocaine concentration of 1.0 mg/L cause a person to become euphoric? Aggressive? Happy? Agitated? What about a concentration of 2.0 mg/L? Would the person experience greater euphoria or become more aggressive? At best, these answers would be speculative, and the ANSI/ASB best practice recommendations (Guidelines for Opinions and testimony in Forensic Toxicology) discourage this type of testimony.[85]

The guidelines also note that one should not calculate the dose of a drug based on a postmortem concentration in blood. There is, however, a formula that may be used in antemortem specimens: Dose (mg) = Body Weight (Kg) x Volume of Distribution (L/Kg) x Blood concentration (mg/L). Because of the numerous variables which may alter postmortem drug concentrations, as described above, this common clinical formula is not reliable for postmortem specimens and can easily lead to misinterpretation.[86]

Questions regarding the physiologic effects of a drug or combination of drugs may arise outside of the courtroom. For example, a family may ask how many pills were taken in a suicide by ingestion. The examination and testing of gastric contents is the most helpful avenue when answering this difficult question. However, in lieu of information regarding gastric contents, the formula for dose determination given above, has been used with caution to give the family a sense of how elevated a particular drug dose may have been. They, however, should be informed of these caveats.

Including all contributing drugs on a death certificate may create some challenges for a prosecutor. The Burrage decision involved a multidrug intoxication death that included heroin and oxycodone. The person who sold the heroin was prosecuted. The Supreme Court ruled that the prosecutor must prove that "but for" the heroin, the person would not have died.[8, 87] The decision stated that the prosecutor did not have to prove that the heroin was the only cause of death, but it must have been the straw that "broke the camel's back." The heroin does not need to be the sole cause, but it must be established that it was "an independently sufficient cause." [8, 87]

Challenges to expertise may occur in court. In general, forensic pathologists are the experts in interpreting a drugs role in a death (interpretive toxicology) while forensic toxicologists are the experts in analytical toxicology. There is, of course, some overlap. Once when Dr. Gettler was testifying in court, he was asked, "Now, doctor, you're really not a doctor, one who treats patients, are you?" He responded, "No, but I have taught hundreds of them."

CONCLUSION:

Forensic toxicology provides objective results obtained through rigorous scientific methods; forensic pathologists can, however, develop a type of "chemical dependence" on reported drug concentrations. As such doctrinaires, a blind, over-reliance on the concentration will result in misinterpretations and missed interpretations. Forensic pathologists must be careful not to

become a slave to a number on a report. As Charles Hirsch said, "routine is never a substitute for judgment."

As described above, there are a variety of investigative, analytical, and interpretive pitfalls that may shine different lights on the toxicology results. Toxicological analyses give us information, but not conclusions. If there are competing causes, the mechanism of death may help point us in the proper direction. And finally, forensic pathologists must clearly and purposefully communicate with forensic toxicologists, the National Center for Health Statistics staff, law enforcement agents, attorneys, and families.

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CHAPTER ELEVEN

In Custody Deaths: Role of Toxicology, Genetics, and Natural Disease

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INTRODUCTION:

Deaths in custody represent numerous situations, types of force, degrees of lethality, intrinsic natural diseases, environmental factors, and other variables. Although these deaths are increasingly captured with various video options, including doorbells, security cameras, officer body cams, and bystander video, critical details and angles may be missing or suboptimal. The sequence and pathophysiologic mechanisms leading to death may require interpretation and professional judgment rather than having clearly defined lethal events, like a firearm or sharp force injury, present and causing the death. These deaths are also extremely public, playing out within raw emotions of racism, deviation from expected equality, individual expectations of law enforcement, and community demands for instant answers.

Restraint-associated deaths seldom occur in isolation. Toxicology findings, natural disease processes, environmental factors, and genetic findings may require consideration. An approach to these problematic deaths is offered here, along with exploring more significant contributions from forensic pathologists in understanding and preventing these deaths. A video of a restraint situation not associated with police action provides a discussion point for these deaths.

MAIN TEACHING POINTS:

1. Discuss the phases of deaths in custody and considerations in each phase
2. Appreciate the role of the forensic pathologist in the evaluation of these deaths, including the role of racism in the conscious and subconscious roots of these arrests and deaths
3. Understand the role of toxicology when examining death in custody
4. Formulate an approach to the interpretation of genetic findings, toxicology, natural disease, and other confounding factors in deaths in custody
5. Identify potential areas and limiting factors where forensic pathologists can improve review and quality improvement in investigating deaths in custody

Case example: A video (without sound) showed a man approaching a receptionist at what appeared to be a car dealership. He seems to be speaking and occasionally moving in a nonpurposeful way with various hand movements. The receptionist is on the phone and turns away from this approaching customer. The customer goes behind the desk and the barrier surrounding the receptionist. After getting no response, he hurls a large bag, later found to be packing peanuts, at the receptionist. She flees and three men come from different directions, subduing the customer and holding him on the ground. There is some movement of the subdued customer for the first few minutes, and then no activity is recorded for the rest of the eight-minute video. Different individuals, primarily men, appear from other business areas; some join the group pinning the customer on the ground. At any one time, two to five men detain the customer on the floor; one individual holds his neck and upper body, another appears to lay across the customer's chest, and occasionally, men from the dealership restrict the hips, arms, and legs of the subdued customer. The men released their hold on the arrival of police, six minutes after the initial subdual. Resuscitation efforts start at the end of the video clip but are unsuccessful.

Autopsy findings include BMI of 31.8 kg/m^2, heart weight of 430 grams, combined lung weight of 1590 grams, soft tissue hemorrhage in the right shoulder, and ecchymosis of the right forearm. Microscopic examination revealed only hypertensive changes. Toxicology revealed caffeine, cotinine, metabolites of THC, Tramadol 91 ng/mL, Chlorpromazine 180 ng/mL, Hydroxyzine 190 ng/mL, Amphetamine 83 ng/mL, and Methamphetamine 1000 ng/mL.

Initial interpretations: Pathologists stated the cause and manner of death from the case video and any other significant conditions as they would fill out the death certificate. Discussion followed, similar to an office quality review; the discussion is the basis for this presentation. Pathologists could modify their case summary and certification and state why they made their assessment.

Dr. Gorniak (original autopsy pathologist):

Cause of Death: Manual strangulation with mechanical asphyxia
Other Significant Conditions: Acute intoxication by the combined effects of tramadol, chlorpromazine, hydroxyzine, and methamphetamine; Probable hypertensive cardiovascular disease obesity
Manner of Death: Homicide

Dr. Sens:

Cause of death: Physical (mechanical) asphyxia due to restraint by multiple individuals
Other Significant Conditions: Combined drug toxicity of tramadol, chlorpromazine, hydroxyzine, and methamphetamine
Manner of Death: Homicide

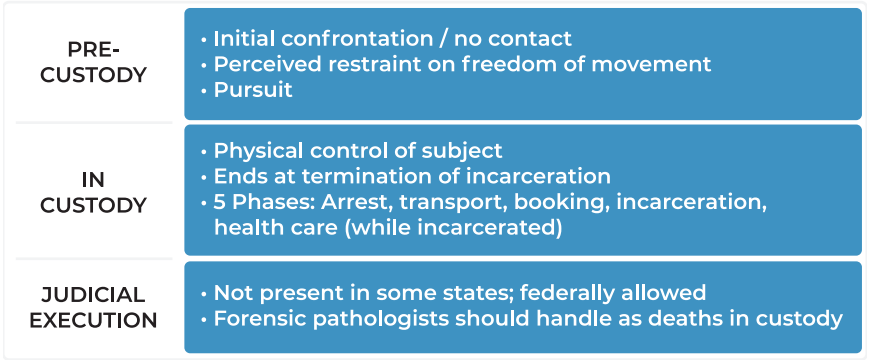
Dr. Wilson:

Cause of Death: Mechanical asphyxia
Other Significant Conditions: [none stated]
Manner of Death: Homicide

All pathologists agreed the manner of death was a homicide and all assigned the cause of death as asphyxia, although there was some variation in wording. There was a different approach to listing other significant conditions, with one pathologist not listing any contributing conditions and the others listing several. No pathologist listed all the compounds found on toxicology examination within the cause of death statement.

Discussion: Deaths in custody are often complex and require detailed assessment for a public inquiry, community justice, and personal resolution. There are several phases of custody, ranging from initial pursuit to death during long-term incarceration. As shown in **Figure 1** (next page), the pre-custody phase involves the initial contact, the perception of the restraint of freedom, and free movement. The contact may be a verbal confrontation, a pursuit, surrounding a location, or other maneuvers to accomplish arrest.

Figure 1.



This phase initiates without physical contact; physical contact starts during this stage, but physical control of the individual is not present. The second phase, in-custody, is a broad and lengthy phase beginning at the time of arrest, when the individual is under the physical control of an officer, and ends when the individual leaves custody, either by release from jail or death. There are subdivisions within this category: arrest, transport, booking, incarceration (in local jail and prison after sentencing), and healthcare during prison terms.

Some individuals argue for parole considerations; however, most acknowledge the difficulty in accurately identifying these individuals and recognize that most death situations are unrelated to custody issues. The final group of custody deaths is judicial executions. In many countries, judicial execution does not exist; however, capital punishment is legal in 27 states, the federal government, and the U.S. military. Forensic pathologists should handle these deaths as deaths in custody and, because of federal offenses, may have capital cases even in states without the death penalty.

Different causes and manners of death are more frequent during various times in custody. Trauma, restraint, toxicology, and natural disease may play a role in any death, including in-custody deaths. In general, natural disease dominates in the long-term prisoners, while trauma and restraint are more commonly observed in the apprehension and subdual custody phases.

The National Association of Medical Examiners (NAME) has a position paper on deaths in custody. This position paper recognizes the difficulty and the broad expanse of these deaths and provides recommendations for autopsy

and certification of these deaths. NAME recommends these deaths be certified as "Homicide" when another individual(s) is involved, particularly in a restraint situation. Although most restraint-associated deaths are best classified as homicide, the position paper recognizes that some cases are quite complex and may be better classified as undetermined or another manner.

The certification is part of an essential public health mandate of the forensic pathologist performing the case. It is distinct and separate from any legal proceedings or investigation and reflects the public health death classification. It should never be utilized to demonstrate support for law enforcement, decedent, or situation, or to influence future civil or criminal action. Death certification should occur independently of the judiciary and law enforcement.

It is critical to acknowledge that these deaths, and the apprehensions from which they result, historically have components of racism and further discrimination involving ethnicity, sexuality, gender, and other classes. Restraint is a necessary component of achieving custody; even with a very passive acquiescence, the arrested individual must have some restraint, such as handcuffs. Instinctive human reaction to restriction of freedom is a "flight or fight" reaction.

Complicating the assessment is the wide range of conditions that may play into the arrest process. Individuals may have mental or developmental challenges and physical restrictions such as hearing loss or reduction. There can be a variety of drugs complicating responses. Individuals may have difficulty understanding English or even a strong regional dialect. Actions, verbal, and nonverbal communication in one culture may vary significantly in another. Actions that are submissive and respectful in one culture may elicit strong negative connotations in another. Without a deep cultural consideration, misinterpretations may have rapidly fatal outcomes in an apprehension–restraint environment.

Natural diseases, genetic conditions, toxicology findings, and environmental factors, individually or collectively, play a role in many deaths, including those in custody; however, there are differences between forensic pathologists in what to include in certification. Although the same considerations may be present in all deaths, in-custody deaths bear a unique chronicle that must be considered for both accurate certification and understanding the divergent opinions of what to include in certification. Historically, when natural disease, toxicology findings, genetic conditions, or environmental factors were listed

as causing or contributing to death, the certification deflected the actions of the police to the conditions of the decedent.

Against the backdrop of racial tension with law enforcement and apprehension, attributing deaths occurring during police action and apprehension to natural disease or accidental effects of drugs the decedent took fails to identify the responsibility of law enforcement, incorrectly blaming the decedent for succumbing to natural disease or drug effect.

This is compounded since many deaths in the pre-custody and early-arrest restraint deaths may have minimal or nonspecific anatomic findings without obvious traumatic injuries such as stab wounds or firearm injury. The death may become entirely ascribed to the natural entity, completely absolving any actions or review of the involved assailants.

Some more common conditions invoked in certification of these deaths that pose a high risk for misinterpretation are sickle cell disease/sickle cell trait, drug intoxication, cardiac conditions, and other potentially fatal natural diseases. Sickle cell disease is a single base pair substitution, autosomal recessive condition of hemoglobin, creating hemoglobin that deforms readily, causing a widespread vascular blockage, extreme pain, and distal ischemia during "crisis periods" when widespread sickling occurs. Although the disease is severe, the heterozygous state, sickle cell trait (SCT), is asymptomatic except in exceptionally rare circumstances. Because SCT confers relative protection against malaria, it is selectively increased in populations originating from the equatorial regions where malaria is common. Sickle cell trait is asymptomatic except in extremely rare cases involving elevated environmental temperature, prolonged, extreme physical exertion, and dehydration causing collapse and pain due to transient sickling in the hypoxic, acidotic individual.

Recognized by military and sports training official decades ago, simple precautions of hydration and periodic rest periods eliminates this complication and thus is rarely seen today. Sickle cell trait should not contribute to any aspect of mortality in restraint deaths unless potentially preceded by extreme and prolonged exertion in the heat with dehydration and metabolic acidosis.

Few in custody deaths would meet this extreme criterion; however, sickle cell trait, a totally benign condition present in approximately 10% of people with African-American ancestry, is listed as the cause of death in many in-custody deaths, invoking a benign and incidental genetic finding as contributing

or causing death, often deflecting any contribution of the individuals exerting fatal restraint. Thus, a listing of SCT or similar genetic variants such as thalassemia or conduction defects without strong, direct evidence of pathophysiologic involvement in death misrepresents medical processes and should not be utilized in death certification.

Drug intoxication is often present in situations leading to custody scenarios. This may take many forms and potential contributions, from bizarre behavior and actions to inability to understand or follow commands and loss of mental acuity and judgment. Drugs, in solitude or combination, provide nearly unlimited potential for interference and behavioral manifestations.

Although individuals can and do die from drug intoxication daily, attributing a death in custody solely or primarily to drug effects requires extraordinary circumstances and investigation. In short, the occurrence of a drug death independent of pursuit, restraint, and custody is extraordinarily rare and virtually impossible to establish.

Certification in a way that emphasizes drug intoxication to the exclusion of other factors is incorrect and does not reflect the public health information necessary from the death certification. There has been a deliberate and concerted effort by lobbyists, consultants, and manufacturers of electromechanical control devices that "Excited Delirium" or "Excited Delirium Syndrome" from a variety of commonly used illicit and prescription drugs independently causes death, absolving law enforcement and any use or effect from the electromechanical devices. This has become so ingrained in the public and law enforcement community that this may be invoked even in situations devoid of substance use. The terms "Excited Delirium" or "Excited Delirium Syndrome" is NOT recognized by leading medical societies, including the American Medical Association and the American Psychiatric Association. The terminology is banned from death certificates in some countries, including the United Kingdom and Australia. There are rare complications of stimulant use, particularly cocaine, where individuals may abruptly exhibit a constellation of symptoms including hyperthermia, extreme disorientation, bizarre behavior, and other signs of psychosis.

Recognized as a hyperadrenergic autonomic dysfunction or acute psychotic drug-related behavioral crisis, these are rare, idiosyncratic responses to some stimulant drugs and represent a true medical emergency, not resistance to authority. Any restraint amplifies the risk of death in this condition; death is

usually precipitous and not responsive to cardiopulmonary resuscitation. In this setting, there is now general agreement that the term, "Excited Delirium", "Excited Delirium Syndrome" or similar wording is NOT acceptable. Although some forensic pathologists prefer to minimize this finding using language such as "Complications of cocaine use," "Acute cocaine intoxication," or other such certification, there is strong support for recognizing this uncommon but known stimulant drug manifestation and utilizing the appropriate medical terminology (i.e., "Hyperadrenergic dysregulation or acute psychosis from cocaine intoxication").

This is analogous to the delineation of the mechanistic path for other deaths (e.g., alcoholic encephalopathy vs. gastrointestinal hemorrhage vs. alcoholic cardiomyopathy, all from chronic alcoholism; or renal failure vs. cardiac failure from systemic lupus erythematosus). The additional information provides a more complete public health assessment and death classification.

The largest group of co-existing conditions that must be considered in restraint-associated deaths in custody is the wide variety of natural disease processes. Individuals may have hypertension, cardiac disease, chronic obstructive lung disease, asthma, diabetes, obesity, and a host of other conditions, many of which increase the chances of sudden death. The forensic pathologist should recognize these, document them within the report, and assess them in full consideration of the death. These conditions should not be primal to determination and the role of restraint, physical or perceived, must always be accounted for. The physical condition and/or diseases of the decedent, in general, are secondary to the restrain or perception of restraint in these deaths, unless some catastrophic, unrelated event occurred such as bilateral saddle pulmonary embolus. The precedent for attributing sudden cardiac death in an individual with severe heart disease under immediate threat, such as a robbery at gunpoint, as a homicide even if physical contact is not made.

This thinking should extend to in-custody deaths, where fear of apprehension may precipitate sudden death from intrinsic natural disease. The manner of death in both scenarios would be homicide.

Individual background and characteristics play a role in the analysis of death in custody. There may be physical handicaps, a variety of mental disorders, loss/reduction in hearing or sight, lack of understanding of English or regional dialect, or cultural considerations that may interplay in these complex situations. Body language meant to convey submission or respect

in one culture may be perceived and threatened or uncooperative in another. All these nuances, and more, are usually present in investigations of these complex deaths.

The complexity and considerations needed for these cases are significant. This formulates an approach to the interpretation of the many facets of a death in custody: how to deal with genetic findings, toxicology, natural disease, and other confounding variables. First, the death certification should represent the best judgment of the forensic pathologist certifier as to what and how the death occurred. This may be challenging in restraint-associated deaths where there may be few if any, physical signs of struggle and no anatomic findings definitive for a mechanism of death.

Given this fact, certification with delineation of restraint is acceptable, even if the exact pathophysiologic mechanism (e.g., cardiac arrhythmia, airway compromise, the integrity of cerebral blood flow, chest compression) cannot be determined. This is not a legal or judicial determination and care should be exerted to emphasize the public health nature of the death certification process and hopefully the independence of the certifier from the judiciary and law enforcement process. Unfortunately, this independence is not present in all jurisdictions, further complicating and clouding objectivity in these cases.

There is relatively uniform support for the appreciation of the difficulty of these cases, the need for complete information, and the desire for substantial inquiry in both the autopsy and the investigation. Most offices support complete toxicology and autopsy with an accurate listing of natural disease, toxicology, and appropriate ancillary testing including genetics within the autopsy report. There is divergence as to what and how much to place on the death certificate.

Some advocate that any information other than the restraint associated with death tends to dilute the assessment and may focus the attention away from the actions of the police or assailant in the death and begin to blame the victim in the death with mention of intoxicating substances or actions. Some forensic pathologists may advocate for extreme detail in the certification, with mention of benign natural conditions, genetic findings of uncertain significance, and listing of all toxicology, including a low and therapeutic range for prescribed medication, urinary metabolites of substances with historical use only and common compounds, such as caffeine, that are present.

This provides full disclosure of information; however, interpretation may be difficult without emphasis on severe conditions. Many forensic pathologists take the middle ground, certifying major, contributory findings and omitting the minor, incidental ones. Regardless of what information is placed on the death certificate, it is important that the certifier 1) be clear as to what caused the death and minimize speculation about minor findings, 2) be objective and not utilize the certification as support or commentary of the appropriate use of force, 3) provide accurate information for public health monitoring and coding of information, and 4) recognize the independence of certification and dissociation from judicial and legal processes.

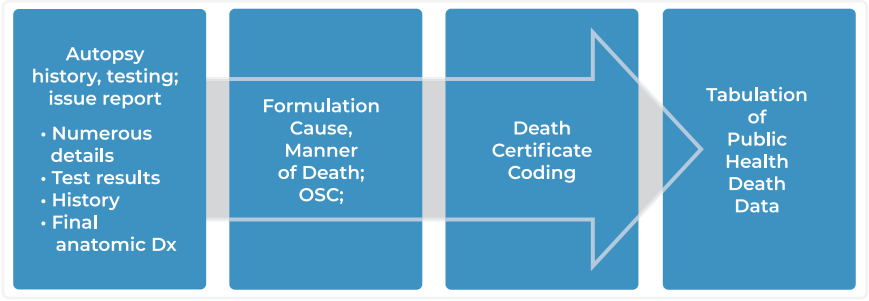
The manner of death in these cases is best considered homicide once contact exists and the actions of another person play into the death. This is not judgmental; actions may be entirely appropriate or they may have full legal culpability. The public health determination of homicide merely confirms the actions of another in the death.

Accidental death or suicide may occasionally be considered. If a person is evading law enforcement, particularly without an aggressive pursuit, and falls, or is involved in a traffic accident or similar misadventure, an accidental manner may be appropriate. It is not uncommon for a pursued individual to commit suicide by a self-inflicted gunshot wound. Although popular for a short while, aggravation of police to return fire is a homicide, not "suicide by cop." Natural deaths would be extraordinarily rare; cardiac events precipitated by the threat of another are generally classified as homicide.

Potentially, an unrelated natural event, like saddle embolism, might be a candidate for natural death certification. It is inappropriate to certify deaths in pursuit and restraint as solely due to natural disease processes even though there may be considerable disease and risk of sudden death. Finally, the NAME position paper recognizes that rarely the situation may be complex with valid competing considerations in death certification. In summary, deaths in pursuit/restraint are homicide unless specific, defensible conditions support another classification. The classification should never be used to suggest support for one party over another or to justify force or actions taken.

A forensic pathologist can enhance the review and interpretation of these problematic deaths, and initiate and lead quality assurance activities to understand and prevent similar deaths. A conceptional vision to identify some potential areas of improvement is given.

Figure 2.



Coding and Clarity: As illustrated in **Figure 2**, the information on the death certificate is coded using the International Classification of Diseases (ICD) leading to the tabulation of types and mechanisms of death. A basic understanding of this coding is critical for public health statistics; the intent of the certifying physician should be clear and represented. Unfortunately, in some areas, coding from what is written on death certificates is not reliably grouped into ICD codes.

In infant deaths, rearrangement of wording may produce final coding for "SIDS/Unexplained death" or "Undetermined death," "Accidental asphyxia from bedclothing," or "pneumonia," and others. Using the tactic in infant deaths of simplification of certification, a theoretical death certificate of "Sudden death due to police restraint" was submitted to code. It was apparent that in ICD-10, the common coding used in the U.S. currently, "restraint" or "police restraint" was NOT recognized and coded since there was no "injury" associated with this on the death certificate using coding algorithms.

Although forensic pathologists could agree that a fatal restraint hold, characterized by one certifier as "asphyxia" and another by "fatal arrhythmia" both describe the same fatal encounter, on certification, asphyxia is recognized as producing injury and would then allow coding of "restraint"; however, "arrhythmia' is not recognized in coding as related to injury; hence, there is no further coding for restraint. Some precipitating conditions from the brain, lung, and cardiovascular system, along with toxins and some metabolic derangements, can produce sudden death and potentially may be utilized in the certification of restraint-associated deaths, particularly those where there are no defined anatomic injuries patterns.

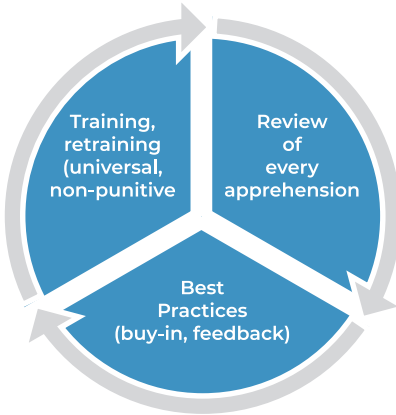
Forensic pathologists and public health must work in concert to assure these deaths are accurately captured as injuries correctly related to restraint.

Quality Assurance: A systems approach to improvement is utilized in a broad range of processes and professions, from manufacturing to banking. Although pathology, particularly clinical pathology was foundational in quality management, medical programs generally were not appreciated until the landmark 1999 study, *To Err, is Human*, by the Institute of Medicine. Professions vary with response and acceptance of quality assurance programs, with aviation generally considered at the forefront of acceptance. The legal and law enforcement communities generally are lagging in this approach. However, with support from forensic pathology and others, a review system may dramatically change the culture of these professions and result in improvements.

Simply stated, a culture of confidential, nonretaliatory, nonpunitive review of basic processes, suggested improvements, implementation, and then a review of outcomes is cyclically examined, leading to improvements with each cycle. Another aspect of success in aviation is the mandated, extensive review of major events, comparable to the "sentinel review" key to quality assurance programs in medicine. In medicine, this review may be triggered by an unexpected outcome such as sudden death during outpatient surgery in a low-risk patient, discharge from the emergency department of a patient having an undiagnosed acute myocardial infarction, or a sitting panel such as Child Fatality Review Boards. In aviation, the trigger is usually the crash of an aircraft. In both medicine and aviation, the review board is broadly constituted of members knowledgeable in the industry and diverse in backgrounds. Specialists may be called as needed. All deliberations are highly confidential, and protected from civil subpoena or other disclosure so members are free to speculate on options and witnesses appear without concern for incrimination.

The panels or boards only make recommendations for systemic improvements and do not have the authority to prosecute individuals. If civil or criminal involvement appears imminent, these panels generally merely refer in general terms to the responsible agency; for example, a hospital peer-review board may recommend the investigation of a particular physician or licensee but will not provide any material or specific information. Standard review of routine processes (**Figure 3**), such as restraint during arrests, regularly and openly reviewed for improvement and training opportunities, would result in increasingly improved systems, presumably safer and more effective for both law enforcement and potential detainees.

Figure 3.



Major events, such as a death in restraint custody, would have a more involved panel review but would improve systems across jurisdictions if properly constituted and accomplished. Forensic pathologists, with a background in quality improvements intrinsic to clinical and general pathology, along with knowledge of quality management in medicine, may be of great assistance in leading initiatives in this area.

Synoptic reporting: The autopsy is the outcome study. The forensic autopsy is rich with detail, observations, measurements, and assessments, from the death scene to external examination to specialty testing and analysis. Nearly all the information is contained in text format; some observations may not be formally recorded yet were a part of the evaluation of the forensic pathologist performing the autopsy. In an autopsy, a modified or additional technique or dissection may be utilized to best demonstrate a finding. There is a vast wealth of information available in an autopsy and that increases with the professional assessment of a highly trained forensic pathologist.

A sentinel improvement in communication of factual reporting came with the development of synoptic reporting, championed by surgical pathologists initially for the increasing complexity of cancer reporting. Like the autopsy, a surgical pathology examination and report on a cancer specimen is also a wealth of information, reflecting training, assessment, and reporting at a high professional level. Surgical pathology reports traditionally were text-based and highly descriptive. As more critical markers in cancer were delineated, these were incorporated in reports but often were difficult to find and occasionally overlooked in text formatted, descriptive, and individualized reports.

The College of American Pathologists (CAP) Cancer Committee devised basic checklists for cancer reporting. These became individualized for each cancer and followed a synoptic format, that is the primary reporting was in the form of pre-set data elements. There was the opportunity for free text but data was in the form of data sets such as:

> **Histologic type:** Adenocarcinoma, Squamous cell carcinoma… (others; may force new fields)
> **Positive lymph nodes:** x positive of Y examined…. (may also include site)
> **Surgical margin:** Positive, negative, not labeled, not examined
> **Surgical procedure:** Biopsy only, excisional biopsy, partial xxx, radical yyy
> **Guidance:** Laparotomy, radiologic guided biopsy, palpation…. (other choices)

These were initially formed for major organs and tumor types. They gained great acceptance and are now greatly expanded, including biomarkers and genetics. Several factors played a role in their success; similar factors can propel forensic pathology synoptic reporting. First, from the data pairs, often with pre-set choices, transcription errors decreased and a comparison of cases was facilitated. Real data were readily available on any number of variables such as lymph nodes examined, size of the tumor, margins, etc. In contrast, forensic pathology has more experience-based assessments (e.g., if one asks about the presence of hemorrhage in hyoid bone or the presence of scleral petechia). Another benefit of synoptic reports was quality improvement.

A study in a large medical center of colonic resections before and after implementation of synoptic reports revealed that 1) more lymph nodes were found by the pathologist when they had to report them synoptically as opposed to somewhere in a text description and 2) surgical margins of the surgeon had a greater incidence of negative findings after synoptic reporting of margins. Thus, both the surgeon and evaluating pathologist improved with synoptic reporting. Other benefits include a better understanding of the disease process involved since objective data is readily available and the needed, regular review of the components of the synoptic report against actual outcomes. This is cumulated by the expert revision of the synoptic form to better understand the underlying disease and positive improvements in ongoing patient care. Synoptic reporting of cancer specimens has grown from an initial two-to-three-page checklist on a few major tumor types to extensive

electronic enumerations for hundreds of tumors, improving reporting and improved patient outcomes. Synoptic reporting is now standard in all surgical pathology with the numerous advantages seen in cancer diagnosis.

Recently, the CAP recommended the use of synoptic reporting for autopsy pathology; forensic pathology will advance when this faster, more rigorous, and reliable reporting is implemented and similar to cancer reporting, regularly reviewed by expert consensus panels for improvements and revisions.

Synoptic reporting of the autopsy, scene, and historical factors may be of great importance to understanding the nature and situations of these deaths. They also can tabulate terminal observations that may play a role in the death without necessarily utilizing pre-defined criteria that may be lacking in objective evidence. For example, rather than jumping to a condition such as hyperadrenergic dysfunction, one could document reported signs, such as core body temperature, the appearance of sweating, incohesive speech, etc.

Care should be taken in the construction of data sets not to prepopulate with racially or gender derogatory choices. For example, individuals under stimulating autonomic psychosis/dysfunction are often referred to as having "intolerance to pain" or "super-human strength". Both these have unfortunate historical references where Black individuals were erroneously thought to have lower pain thresholds and greater strength, resulting in unacceptable exposure to pain and/or cruelly physical work conditions of slavery or indenturement. A more objective measure of this might be several electromechanical hits without apparent reaction or an objective measurement of individuals picking up adults, cars, or other objects without apparent stress. A properly constructed synoptic inquiry can provide real, objective data needed to sort through these complex deaths and lead to improvement of policies and reduction of deaths and morbidity.

Family obligations: Finally, the forensic pathologist must remember their duty to the decedent and the family. Information to the family should come from the forensic pathologist, not the press. Be truthful and honest with the family who is mourning the loss of a loved one in addition to whatever public information and situations arise. Directly communicate with the family, express sympathy, and explain what you can. This may be relatively straightforward in systems independent of judiciary and law enforcement. It may be challenging in other systems which may attempt to insert nonmedical personnel, public relations personnel, or law enforcement/judiciary representatives.

In many cases, there will be consultants and requests for second, third, or other autopsy reviews. Ideally, these should demonstrate mutual respect and professionalism to all concerned. Deaths in custody are highly reviewed and emotionally charged deaths, particularly in the pre-custody, restraint phase without the use of lethal weapons such as firearms. In most forensic offices, these cases are automatically subject to quality review by others; if not, the forensic pathologist performing these autopsies should make these a quality reviewed case with others in the office, seeing opinions and interpretations. The forensic pathologist should also consider consultation outside the office with other forensic pathologists to assure complete considerations needed in these complex cases. In most instances, expanded toxicology, possible genetic testing, and specialty consultations should be considered. If feasible, supporting wider review panels to improve the systems approach is desirable.

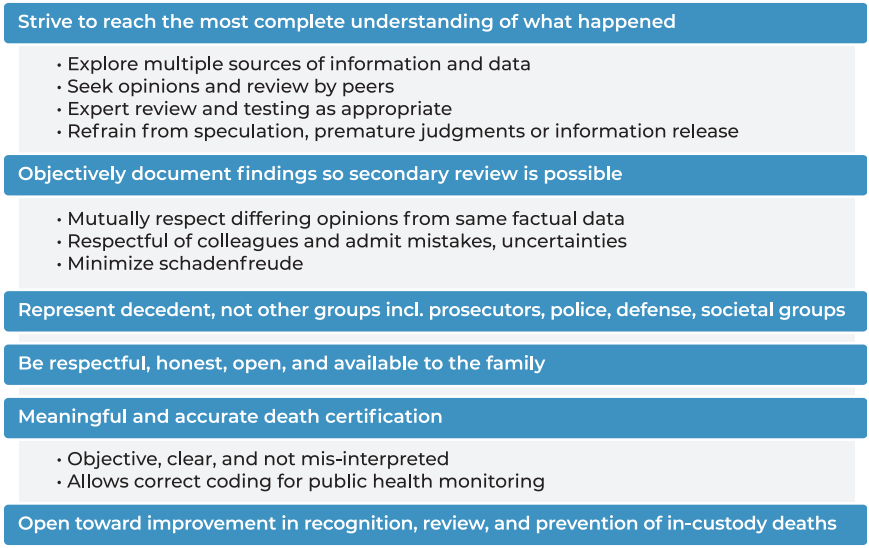
Professionalism: Finally, the forensic pathologist should remain professional and collegial in the discussion and review of cases. Opinions and interpretations may evolve with discussion. Admit uncertainties, consider alternatives, and minimize schadenfreude. In consideration of this openness to discussion and review, the original pathologists were asked to re-evaluate their initial interpretations in this case. As expected, although there was substantial agreement in the initial certification, the revised certifications tended to harmonize in the middle.

Part one was unchanged by all physicians and as previously discussed, all agreed on asphyxia-related death utilizing differing but analogous wording. All initially agreed homicide was the best classification of manner of death and this was not changed. In Part II, other significant conditions, there was the most change. Both Dr. Gorniak and Sens focused the certification to only include major conditions capable of producing death (i.e., methamphetamine intoxication), with Dr. Gorniak dropping hypertension and obesity, Dr. Sens dropping obesity and hydralazine use. Dr. Wilson did not add methamphetamine intoxication to her certification; however, she supported forensic pathologists who did add this in Part II.

CONCLUSION:

Death certification is challenging, particularly in the case of restraint-associated deaths without definitive trauma. Important concepts are listed in **Figure 4**.

Figure 4.



Many individuals have serious comorbid conditions including potentially lethal diseases, drug intoxication, and genetic profiles that increase the risk of sudden death within certain environmental conditions. The deaths often have a high public profile, pressure for instantaneous results, and active discussions on social media. Many occur in a racially charged atmosphere, the restraint actions may be questioned, and the decedent's comorbidities may be substantial.

The forensic pathologist must certify these deaths to be deliberate and objective and not use the certification to "absolve" or support actions. It is important to be cognizant of past inequities of restraint situations and professionally respectful to variations that will occur between qualified individuals. The autopsy report should contain details of extensive testing, observations, and documentation fundamental to the autopsy. There are ways, such as synoptic reporting, that may make this more facile and organized in the future but the place for most toxicology, genetic results, and natural disease patterns is within the autopsy report. The use of a summary section within the autopsy report is also highly recommended so that the thought process and consideration are clearly articulated.

This summary component is not uniformly taught in some forensic training; however, it is recommended in infant deaths by the SUDPEDS panel from

NAME because of the complexity present. In custody deaths, particularly restraint deaths, are an equivalent or higher level of complexity and need articulate communication, hence the summary recommendation. Death certification should reflect the cause of death in the best judgment of the forensic pathologist; one should be cognizant of coding and classification so that injury is readily recognized within the words used. Restraint may be a component of both the certification in Part 1 and 2 as well as in the descriptive phase of "How the injury occurred."

When potentially lethal toxicology findings or natural disease is present, an objective listing of this within both the autopsy report and death certificate is desirable, but care should be taken not to overshadow the restraint component or to attempt to justify the actions of law enforcement. As recommended by the NAME position paper, most of these deaths should be certified as homicide; the summary section within the autopsy report can serve as a template for the thinking and justification used in the certification. There will be some variation between equally qualified certifiers and professional acceptance and discourse in the discussion of these complex deaths is crucial for public discourse and policy. Honest and open family communication, independent and ideally before press releases, is essential, and the need for independence of the forensic pathologist from both law enforcement and the judiciary system is vital.

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Chemical Asphyxiants

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INTRODUCTION:
Sodium nitrite began to gain public attention partly as a result of the dramatic mystery presented in the book, *Eleven Blue Men,* by Burton Roueché.[1] The short story was originally published in the *Annals of Medicine* in 1948, detailed a series of New York City men who ate oatmeal at a diner and then became cyanotic, and was brought to the attention of the Department of Health. The chef mistook sodium nitrate for sodium nitrite and inadvertently added this chemical asphyxiant to the meal.

The rare reports of sodium nitrite ingestion up until the 1980s were mostly groups or families that had accidental sodium nitrite ingestions. From that time, the ingestion of sodium nitrite moved from unintentional into intentional ingestion as a suicidal agent. However, the access to these methods was effortful, as nitrites were not readily available for most. Although there was continued use and notoriety to barbiturates such as pentobarbital, also known as "yellow jackets," asphyxiants began to emerge as possibilities for euthanasia and suicide. Much of this shift seemed to result from books such as the *The Peaceful Pill Handbook* and *Final Exit* and the cultural shifts in ideas and collectives around physician assisted suicide.[2]

Societies such as the Hemlock Society of San Diego (formed in 1980) were advocates of such shifts in thought. The global AIDS epidemic coincided with euthanasia movement and news outlets such as National Public Radio's Frontline Series on the evolution of America's "right to die" movement detailed controversial processes and access of populations of AIDS patients to suicidal agents and methods.

Suicide is continually examined and many theories discuss coupling versus displacement. In the book, *Talking to Strangers* by Malcolm Gladwell, coupling was highlighted as there was a decrease in suicides in the United Kingdom when coal heat was switched to gas heat.[3,4] There was not an immediate displacement to another option. In the current global market, access to most agents is achievable and suicidal methods are varied as such with increase in asphyxiants.

MAIN TEACHING POINTS:

1. Asphyxiants can be classified as chemical or simple asphyxiants and both result in tissue hypoxia.
2. Chemical asphyxiants are those that interfere with oxygen transport or absorption of oxygen resulting in cellular hypoxia.
3. Simple asphyxiants displace oxygen from ambient air.

Chemical Asphyxiants: Nitrites and Nitrates

Sodium nitrite is a very powerful oxidizing agent and is used mostly as salts, pesticides, antimicrobial agents, and as food preservative. Sodium Nitrate is also an oxidizing agent, albeit at a much less powerful than nitrite, and can also be a reducing agent. It is also known as saltpetre. Sodium nitrate is a curing agent to help retain that very pink color in meat and can be used as a fertilizer and in pyrotechnics and glass making. Nitrates are also organic and involved in the enterosalivary circulation of nitrates in humans.[5]

Ingestion of nitrates are converted by anaerobic bacteria in the salivary glands and our intestinal lumen into nitrites, and the nitrites will go into circulation and produce free radicals and some nitric oxide. The basal level of nitrites will result in usually less than 1% methemoglobin. The hemoglobin molecule is comprised of four globin molecules, each with a pocket that binds the heme group, which reversibly binds oxygen. In the ferrous state, the heme moiety can easily release oxygen into the tissues. When there is an excess amount of nitrates/nitrites, the iron will be in the ferric oxidized state and the molecule is known as methemoglobin. Methemoglobin has a decreased ability to bind

oxygen and causes a left shift in the oxygen dissociation curve, with resulting tissue hypoxia. The mechanism of hypoxia in nitrite intoxication is actually two-fold: not only does cause an inability to bind oxygen but on the cellular level, but the production of nitric oxide also binds to cytochrome c, inhibiting mitochondrial respiration.

Currently, most sodium nitrite intoxications are in the context of suicide.[6,7] At the scene, a bottle of sodium nitrite may or may not be found at a scene depending on whether or not the decedent managed to conceal the ingestion or concealment happened by those who found the decedent. A cup with a white slurry is typically of the mixture. In accidental exposures, reports detail a variety of scenarios including those where the nitrites are erroneously labeled as sodium chloride and subsequently used for cooking. In those scenarios, a family or a group of individuals may be symptomatic. If a suicide kit has been purchased by the decedent, it may include an antacid or antimotility agents such as metoclompramide to prevent vomiting. Other scene findings that are consistent with intentional ingestions include books such as *Final Exit* or the *The Peaceful Pill Handbook*.

Clinically with nitrite intoxication, persistent cyanosis despite supplemental oxygen therapy as well as gastrointestinal discomfort is the rule. Hypotension and arrythmias may occur due to nitric oxide production. There is predictable progression of signs and symptoms that correlates to the level of methemoglobin concentrations. Cyanosis with skin discoloration and brown blood will be seen around 10% and then at 50 to 70% comes CNS depression and lactic acidosis, metabolic acidosis, and seizures, with subsequent death. Recipes for sodium nitrite intoxication can be found on websites such as www.sanctionedsuicide.com.

In infants, there are inherited and congenital disorders where elevated methemoglobin is found specifically related to cytochrome b5 reductase deficiencies.

The acquired states of methemoglobinemia due to nitrite toxicity include ingestions of isosorbide dinitrate, nitroglycerin, potassium permanganate, ammonium nitrate, and globally, especially in areas in India, where drinking water has elevated nitrates/nitrites due to agricultural runoff. Methemoglobinemia due to the non-nitrite pathway includes excess oxidative states such as sepsis, ingestion, or exposures to benzocaine and other anesthetics.

Nitrite intoxication with methemoglobinemia has characteristic autopsy findings such as cyanosis in light skinned individuals, resulting in blue-gray discoloration of the skin, especially in areas of lividity. The internal examination will show skeletal muscle with a bright red, cured appearance and can be helpful in darkly pigmented individuals when the slate gray discoloration is not apparent on external examination. The blood will have a deep maroon or dark brown appearance that persists even if exposed to oxygen. Postmortem toxicology testing for diagnostic purposes is challenging as one sees artifactual increases and decreases in methemoglobin levels due to either reductase activity by bacteria or auto-oxidation during storage.[8] Mixed Nitrate/nitrite concentrations can be measured with a fair degree of sensitivity.[9] Co-ingestions are to be expected in suicidal ingestions including high level of antiemetics such as metoclopramide.

Amyl nitrites are commonly known as "poppers" and are not infrequently found in stores nearby night clubs or associated with a party culture. Amyl nitrite poppers have a deep history in New York City and San Francisco associated with gay culture. Amyl nitrites are alkyl nitrates and are commonly prepared as volatile substances meant to be inhaled but ingestions and rare fatal intravenous intoxications are reported in the literature.[10]

Amyl nitrites are no longer under FDA approval and instead are monitored under Consumer Affairs as they are commercially marketed as nail polish remover, air fresheners, deodorizers, or liquid incense. The initial medical use was for angina with a vasodilatory effect. There are many reports of intoxications with the early reports detailing autoerotic scenarios with towels soaked in amyl nitrite.

In the early seventies, medical articles associated the risk of methemoglobinemia with "avant-garde heterosexuals" or men who have sex with men. They describe a transient euphoria associated with relaxation of the anal sphincter. Erroneously, studies during the early HIV/AIDS epidemic, when the pathophysiology of AIDS was not known, linked poppers to immunosuppression with low white blood counts in patients who used amyl nitrite.[11]

The mechanism of intoxication is similar for amyl nitrite as sodium nitrite. There may be a larger vasodilatory effect related to the nitric oxide production. Clinically, one may experience reactive airway disease as these are inhaled or dermatitis and reactions to the eyes with glaucoma and temporary vision loss. Rare hemolytic anemia reactions are reported, particularly if ingested.

Although the lay press describes "sudden sniffing death," these are usually not associated with amyl nitrite but instead, halogenated solvents. Combined effects of alcohol and/or with amyl nitrite leads to a marked hypotensive state.

Simple Asphyxiants: Inert gases that are simple asphyxiants and commonly present as suicidal agents are helium, argon, and nitrogen. In general, inert gases include krypton, neon, xenon, and radon.

Helium is a colorless, tasteless, nonvolatile, and nonexplosive gas that is seven times lighter than air and is the second most abundant element in the universe. The helium that is found in canisters is sourced from underground along with natural gas. The availability of helium can fluctuate, which may have a coupling effect in terms of suicidal agents. The main national sources of helium are Texas and Wyoming. Helium has both recreational and medical uses such as heliox, which is a mixture of helium and oxygen that may be used for respiratory diseases such as croup and is a coolant for magnetic resonance imaging magnets.

Most canisters are pure helium; however, from the forensic perspective, one can imagine a case that may show multiple mechanisms other than asphyxia if the canisters have a mixture of helium and oxygen and don't produce the desired effect.

The urge to breathe in humans is controlled by blood pH related to the carbon dioxide concentration, which is constantly monitored through chemoreceptors. Elevations in carbon dioxide will drive the urge to breathe. Replacement of air with a simple asphyxiant will displace oxygen and reduce the percentage of oxygen in the air. In order for this to be effective at producing hypoxemia, these agents have to be at a very high concentration. For this reason, plastic bags or confined spaces are needed to actually produce asphyxia with hypoxemia and death. With inert gases, there is no hypercapnic alarm to increase the respiratory rate, as there is no concomitant increase in the carbon dioxide level, with loss of consciousness occurring in about twelve seconds.

In intentional asphyxia cases, the scene findings may have a helium or other asphyxiant gas tank in the room with the body and a plastic bag will either be over the head or may have been taken off by a family member or first responder. Concealment by family or kin can occur and in those cases the diagnosis can be very difficult.

A suicide bag can be purchased online or a generic plastic or garbage bag can be used for the hood, where it is rethreaded and the thread has a simple loop. The tubing will be underneath into the bag, and then the connected to the helium tank or other gas.[12] Most cases will be one individual but there are rare reports of dyads (suicide pacts) or groups.

In general, in plastic bag asphyxia, there are no petechiae unless the bag fastener is as tight as a ligature. In most cases, the gas in the bag will rise and the bottom is not needed to be tight about the neck to reach high inert gas concentrations.[13] Carbon dioxide can be a simple asphyxiant and may be seen in unintentional intoxications. An online influencer intended to fill a pool with smoke using dry ice. When the ice was added to the pool by two helpers, it sublimated and the carbon dioxide was released at a high level and resulted in asphyxia. Particularly during sublimation in water, carbon dioxide is actually very dense, and if a person is on the floor, very high concentrations of carbon dioxide can be achieved and result in asphyxia.

Toxicology analysis is very challenging in these cases of simple asphyxiants, as gases such as helium is a common carrier gas in toxicology instruments. Various articles discuss that one can switch to nitrogen carrier gas if trying to measure helium and collect samples in a headspace file with a rubber top. Testing the tank from the scene can also be useful if the identity of the gas is in question.

Once rare in the early part of the 2000s, simple asphyxiants are becoming a more common method for suicidal plastic bag asphyxia. In one study, by the end of 2012, simple asphyxiants represented 40% of the suicidal agents, moving away from carbon monoxide.[14]

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