



Academic Forensic Pathology

The Official Publication of the National Association of Medical Examiners

J. Keith Pinckard MD PhD EDITOR-IN-CHIEF
Nicholas I. Batalis MD ASSOCIATE EDITOR-IN-CHIEF



The Opioid Crisis

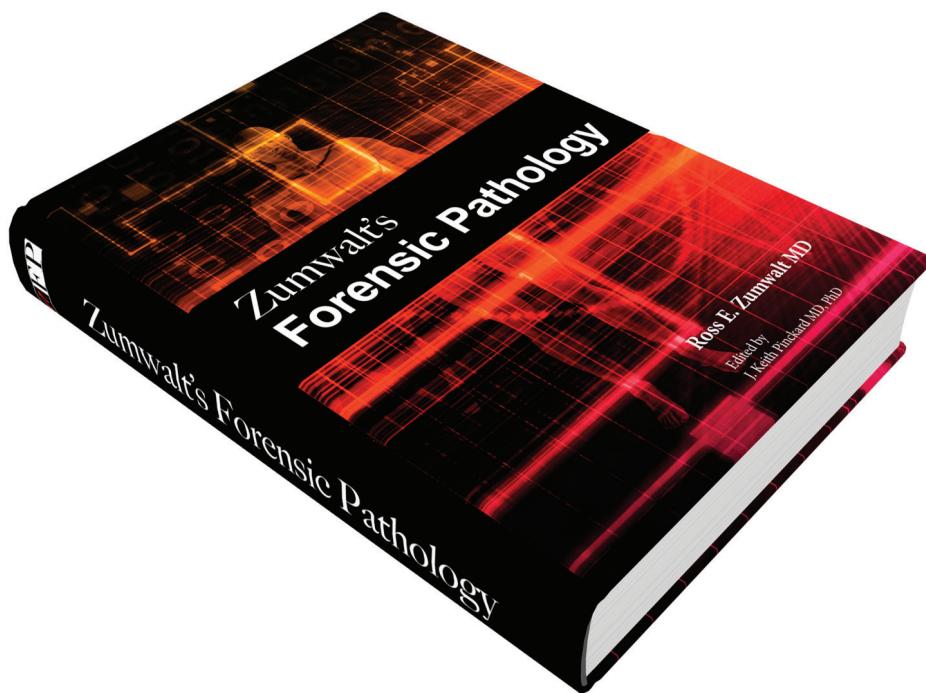
Volume Seven • Issue One • March 2017

Dr. Zumwalt practiced forensic pathology for 40 years — instead of practicing one year of forensic pathology 40 times...

A book about HOW and WHY we practice the way we do, and how to GROW as we practice...

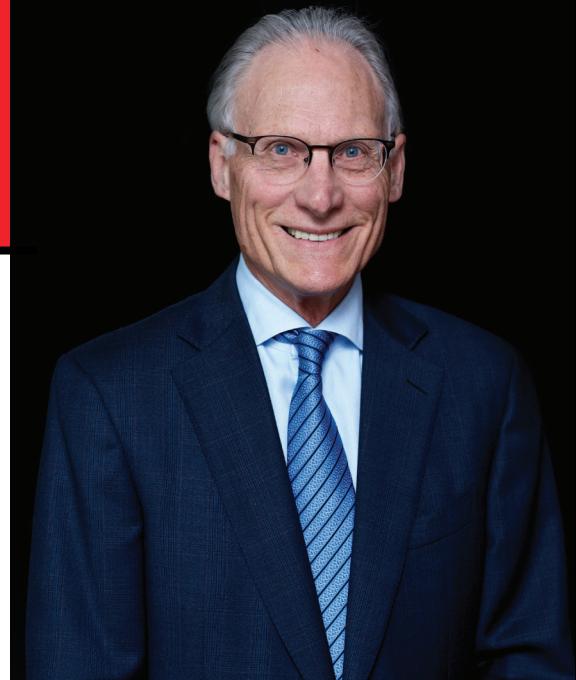
**PRE-ORDER BY MAY 31, 2017
TO SAVE \$100**

<https://store.academicfp.com>



Foreword by Randy Hanzlick MD

Published by Academic Forensic Pathology International



Ross Zumwalt MD

(Former) Chief Medical Investigator
New Mexico OMI

Zumwalt's Forensic Pathology includes:

- *Death certification*
- *Death investigation*
- *The forensic autopsy*
- *Ancillary laboratory studies*
- *Apparently natural death*
- *Apparently accidental death*
- *Apparently suicidal death*
- *Apparently homicidal death*
- *Deaths whose manner cannot be determined*
- *Other topics*

Approximately 500 pages

Published in brilliant full color

Estimated release: Fall 2017

Full retail price \$350 USD



On the Cover

"Red poppy on a black background." Used under license from www.shutterstock.com.

On the Scholarly Content Cover Page

Front matter description of scholarly content cover page: stylized 40 power photomicrograph of polarized, refractile material in a lung.

Editor-In-Chief J. Keith Pinckard MD PhD

Associate Editor-In-Chief Nicholas I. Batalis MD

Special Guest Editor Thomas P. Gilson MD

Publisher Emma O. Lew MD

Executive Director Evan W. Matshes MD FRCPC

Director of Operations Don Downey BA PMT

Editorial Director Lori Selanders BSc MSc

IT Consultant Alex Kiriako

Research Associate Kacy Krehbiel MD

Medical Illustrator Diana Kryski

Web Designer and Programmer Kimm Wiens

Executive Offices

7946 Ivanhoe Avenue, Suite 107
La Jolla, CA
92037
1-888-909-7856

email admin@academicfp.com

www.academicfp.com

www.afpjournal.com

<https://store.academicfp.com>



Editorial Board Members

Russell T. Alexander, MD, Assistant Medical Examiner, Office of the Chief Medical Examiner, State of Maryland, Baltimore, MD, USA

Sam W. Andrews MD, Deputy Medical Examiner, Travis County Medical Examiner's Office, Austin, TX, USA

Jonathan L. Arden MD, President, Arden Forensics, PC, McLean, VA, USA

Jim Caruso MD, Chief Medical Examiner, Denver Office of the Medical Examiner, Denver, CO, USA

David Fowler MBChB MMed Path (Forens), Chief Medical Examiner, Office of the Chief Medical Examiner, State of Maryland, Baltimore, MD, USA

James Gill MD, Chief Medical Examiner, Office of the Chief Medical Examiner, Farmington, CT, USA

Michael Graham MD, Chief Medical Examiner, City of Saint Louis; and Professor of Pathology, Saint Louis University, Saint Louis, MO, USA

Kathy Pinneri MD, Director, Montgomery County Forensic Services, Conroe, TX, USA

Leslie E. Hamilton MD, Neuropathologist/Autopsy Pathologist and Neuropathology Residency Program Director, Calgary Laboratory Services and University of Calgary, Calgary, AB, Canada

Jennifer Hammers DO, Deputy Chief Medical Examiner, Brooklyn Campus, Office of the Chief Medical Examiner, New York, NY, USA

Walter Kemp MD PhD, Associate Professor, University of North Dakota School of Medicine and Health Sciences, Grand Forks, ND, USA

Laura D. Knight MD, Chief Medical Examiner, Washoe County Regional Medical Examiner's Office; and Associate Professor, Departments of Pathology and Pediatrics, University of Nevada-Reno School of Medicine, Reno, NV, USA

Kelly C. Lear-Kaul MD, Coroner/Forensic Pathologist, Arapahoe County Coroner's Office, Centennial, CO, USA

Owen Middleton MD, Assistant Chief Medical Examiner, Hennepin County Medical Examiner's Office, Minneapolis, MN, USA

Christopher Milroy MD LLB LLM FRCPath FRCPC DMJ, Director of Forensic Pathology, Ontario Forensic Pathology Service, Ottawa, ON, Canada

Marcus Nashelsky MD, Clinical Professor of Pathology, University of Iowa Hospitals and Clinics; and Chief Medical Examiner, Johnson County Medical Examiner's Office, Iowa City, IA, USA

William R. Oliver MD, Assistant Medical Examiner, Regional Forensic Center, Knoxville, TN, USA

Reade Quinton, Deputy Chief Medical Examiner, Southwestern Institute of Forensic Sciences, Dallas, TX, USA

Robert Stoppacher MD, Chief Medical Examiner, Onondaga County Medical Examiner's Office, Syracuse, NY, USA

Victor W. Weedn MD JD, Professor, Department of Forensic Sciences, Washington University, Washington, DC, USA



TABLE OF CONTENTS

AFP

ACADEMIC FORENSIC PATHOLOGY:

The Official Publication of the National Association of Medical Examiners

March 2017 • Volume Seven • Issue One • The Opioid Crisis

EDITORIALS

| | |
|--|-----------|
| Letter from the Editor-In-Chief | vi |
|--|-----------|

J. Keith Pinckard

| | |
|---|-------------|
| Letter from the NAME President | viii |
|---|-------------|

Brian L. Peterson

| | |
|--|----------|
| Letter from the Guest Editor..... | x |
|--|----------|

Thomas P. Gilson

INVITED REVIEWS

| | |
|---|----------|
| Drug Intoxication and the Need to Autopsy: A Diagnosis of Exclusion? | 2 |
|---|----------|

David R. Fowler

| | |
|---|----------|
| Confronting an Upsurge in Opiate Deaths With Limited Resources | 7 |
|---|----------|

Thomas A. Andrew, Jennie V. Duval

| | |
|-----------------------------|-----------|
| Opioid Toxicity..... | 19 |
|-----------------------------|-----------|

David Dolinak

| | |
|---|-----------|
| Emerging Synthetic Fentanyl Analogs..... | 36 |
|---|-----------|

Harold E. Schueler

| | |
|---|-----------|
| The Evolution of the Opiate/Opioid Crisis in Cuyahoga County | 41 |
|---|-----------|

Thomas P. Gilson, Hugh Shannon, Jaime Freiburger

| | |
|--|-----------|
| Opioid Drug Death Investigations..... | 50 |
|--|-----------|

Daniel Morgan

| | |
|---|-----------|
| Drug Overdose Surveillance and Information Sharing Via a Public Database: The Role of the Medical Examiner/Coroner | 60 |
|---|-----------|

Karl E. Williams, Michael D. Freeman



TABLE OF CONTENTS

AFP

The Utility of a Prescription Monitoring Program in Death Investigation: The Virginia Experience73

Amy M. Tharp-Myers, Kathrin Hobron, Ralph Orr

County Coroners and Their Role in the Heart of the Opioid Epidemic80

Renee Robinson

Rules for Establishing Causation in Opiate/Opioid Overdose Prosecutions — The Burrage Decision87

Thomas P. Gilson, Carole Rendon, Joseph Pinjuh

ORIGINAL ARTICLES

Common Findings and Predictive Measures of Opioid Overdoses91

Danielle E. Pelletier, Thomas A. Andrew

Gabapentin in Mixed Drug Fatalities: Does This Frequent Analyte Deserve More Attention?99

Grant Finlayson, Michael Chavarria, Stephanie Chang, Tyler Gardner, Abigail Grande, Colleen MacCallum, Joyce L. deJong, Kelly Quesnelle

Primary Cardiac Tumors in Infancy: A Case Report and Literature Review112

Carolina Dominguez, Ashley Perkins, Alexandra Duque, Viagnney Bravo

Blastomycosis in Wisconsin: Beyond the Outbreaks119

Katrina Thompson, Alana K. Sterkel, Erin G. Brooks

CASE OF THE MONTH

Fatal Rotavirus Infection in a 4-Year-Old with Unsuspected Autoimmune Adrenal Insufficiency.....130

Alison Krywanczyk, Elizabeth A. Bundock

A Case of Previously Unsuspected Huntington Disease Diagnosed at Autopsy.....136

Catherine R. Miller, Nobby C. Mambo, Jianli Dong, Gerald A. Campbell



TABLE OF CONTENTS

AFP

COPYRIGHT NOTICE

This publication and its content is copyright of Academic Forensic Pathology International ©2017. All rights reserved.

Subscribers may download and print-off Journal articles for their own personal use. Subscribers may distribute articles for scholarly purposes only. Subscribers may not receive payment in exchange for reproducing an article published in the Academic Forensic Pathology journal. As per the AFPi Author Rights (see below), although an author assigns AFPi copyright of their manuscript, they retain the right to use, teach with, and in a limited fashion distribute their manuscript for scholarly purposes. However, any individual, group, institution or corporation who does not have authorship over an AFP Journal article, but intends to distribute that article in any fashion (including distribution at meetings, educational sessions, etc.), must obtain an offprint license from AFPi directly or risk copyright violations. Inquiries should be directed to the Publisher.

Authors retain the following rights:

1. The right to make print or electronic copies of the article for their own personal use. Personal uses extend to the classroom where an author is granted the right to distribute print or electronic copies to students.
2. The right to distribute print or electronic copies of the article to colleagues, strictly for scholarly use. This expressly excludes commercial uses including fee-for-service consultations. The author may not receive any form of payment in exchange for provision of a print or electronic copy of the article.
3. The right to present the substance of the article at scientific meetings and to distribute a copy of that article to meeting attendees.
4. The right to provide a copy of the article to the author's employer or home institution.
5. The right to prepare derivative works from the article, including books, so long as full acknowledgement of the original publication is provided.

DISCLAIMER

The Publisher (Academic Forensic Pathology International), The Editor-In-Chief (Dr. Keith Pinckard) and the sponsoring society (National Association of Medical Examiners) are committed to the publication of high quality, timely and relevant scholarly forensic pathology materials, and take every effort to ensure that the information presented within the Journal are precise and accurate. However, errors can occur and readers must carefully evaluate the literature and decide how to best integrate it into their own practice. Please report any errors directly to the Publisher (publisher@academicfp.com) or the Editor-In-Chief (editor@academicfp.com). The Publisher shall not be liable or responsible for any direct or indirect losses or damages of any kind whatsoever, whether based in contract, tort, strict liability, or otherwise, arising out of or in any way connected with: your use of or inability to use this website; the provision of or failure to provide services; any information, products, services, software or graphics obtained through this site. The Editor-In-Chief and the Publisher do not assume any responsibility for any injury and/or damage to persons or property related to any use of the content contained herein. Publication of an advertisement or other product mention in Academic Forensic Pathology: The Official Publication of the National Association of Medical Examiners is not an endorsement of either the product or the manufacturer's claims and should not be construed as such.

A toxicology book written by a forensic pathologist for forensic pathologists

Forensic Toxicology: A Physiologic Perspective

- An easy-to-read text that explains how various drugs, toxins, and combinations thereof can prove toxic and cause death, while addressing many of the factors to be considered when interpreting postmortem drug concentrations

- Find out about new designer drugs
 - an ongoing challenge for forensic toxicologists

SALE 50% OFF

Use Coupon Code: **TOX50** and receive 50% off the US\$150 purchase price.

*Limited time offer. Coupon code Expires February 15, 2017. May not be combined with any other offers. Previous purchases do not qualify.

- Learn that numbers don't kill people - drugs kill people - finally a book that focuses on how, when and why drugs kill, and not the numbers prepared for tox reports

- Evaluation of a particular drug concentration is just one factor in a complete case investigation - find out what other information the forensic toxicologist must take into consideration in toxicology-related deaths

David Dolinak MD • ISBN: 978-0-9879053-1-4 • 456 pages • \$150.00

Free shipping within North America

<http://store.academicfp.com>

Letter From the Editor-In-Chief

A handwritten signature in black ink, appearing to read "J. Keith Pinckard".

J. Keith Pinckard MD PhD
Editor-In-Chief

The theme of the first issue of 2017 is “The Opioid Crisis” and the Special Guest Editor is Dr. Tom Gilson. I believe that “crisis” is an appropriate description of the opioid problem facing the nation. Prescription drug abuse and toxicity have skyrocketed in recent years, especially with the emergence of fentanyl and fentanyl analogs and their introduction into clandestinely produced opioids, including both heroin and other “counterfeit” prescription opioids.

This crisis, along with the profoundly increased numbers of opioid-related deaths, has affected medicolegal death investigation systems in an unprecedented man-

ner. Offices are becoming overwhelmed with keeping up with the increased numbers of drug-related deaths to the point that they are needing to hire more death investigators and forensic pathologists. Some offices, however, are not sufficiently supported or funded, and thus, the crisis creates a threat to accreditation as well.

We begin with a pair of articles. The first discusses the need to autopsy all drug-related deaths in order to best serve the public. The second, while acknowledging the desire to function in this way, presents a temporary solution for those who cannot autopsy every potential drug-related death at this time. The next two papers



are reviews on the mechanisms of opioid toxicity and of the emerging family of fentanyl analogs. We then feature a paper discussing the evolution of the opioid crisis in one particular jurisdiction. There is also a paper discussing the medicolegal death investigation of potential drug-related deaths. We have a paper describing the public sharing of information involving the medical examiner and another discussing the benefits of prescription drug monitoring programs for medical examiners. There is also a paper discussing particular challenges for coroner systems in the opioid epidemic. Finally, we feature a paper discussing the role of the Burrage decision in criminal proceedings. We also feature several original articles, two of which address issues relevant to the opioid crisis, and two “Case of the Month” papers.

The second issue of 2017 will be released on June 1; the theme will be “The Death of SIDS” and the Special Guest Editor will be Dr. Melissa Pasquale-Styles. But remember, only about half of each issue is devoted to the specific theme. It’s really just a way to promote submission of articles on a particular topic. Manuscripts about any topic can (and should) be submitted at any time! As always, I will continue to encourage the readership to submit articles to the Journal. We depend on submissions from the readership—NAME members like you—to sustain our excellent content.

Letter From the NAME President



Brian L. Peterson MD
NAME President 2017

It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair...

So begins *A Tale of Two Cities*, and Charles Dickens' words seem equally applicable in 2017. Are these the best of times for death investigation in general, and forensic pathology specifically? Surely at least, not bad. Our science continues to improve, year by year. We enjoy an efficient and effective division of labor, with trained, credentialed death investigators "out there" attending scenes, and subspecialty trained forensic pathologists "in here" performing autopsies. Although our numbers are not huge, thanks to cooper-

ation with larger like-minded groups such as the College of American Pathologists we have achieved some marvelous victories; the changing landscape of Maintenance of Certification/Self-Assessment Modules comes to mind. From *CSI* to Hollywood to Amazon best-sellers, our field is well-known to the public—or at least they think they know—and perceptions are generally favorable.

At the same time, focusing on this issue of *Academic Forensic Pathology*, we are somewhere between a deluge and a tsunami of opioid-driven death that threatens to overcome us. Take a baseline of drug abuse—cocaine and heroin, with the occasional exotic such as phencyclidine thrown in. Mix in very effective marketing of a former second tier drug, oxycodone, and a hard push by government, credentialing agencies, and



advocacy groups to make pain the “fifth vital sign.” Layer on patient expectations for smiley faces and lives free of any pain, and finally add a dash of changing prescribing practices that will predictably drive long-term prescription opioid users to the street—and we have a perfect storm of overdose death. Case numbers and laboratory burdens explode even while inexpensive potent analogs of fentanyl reach our shores by the ton. Office accreditation is imperiled by case numbers while formerly serviceable screening methods such as ELISA are rendered ineffective due to the regular import of novel analogs. How is our profession to respond?

Well, back to optimism. This issue of *AFP* will be an effective tool; given that the lethal drug mix varies by neighborhood, city, county, and state, here is timely information with which we all need to become familiar. Our colleagues may face a different mix of drugs, but we are all confronting the same root issue. And what we report, the government at many levels

is beginning to acknowledge as well. Perhaps the silver lining here will include increased recognition of the importance of our work, increased funding, and an increased emphasis on regionalization that will make better use of our small numbers. Ultimately, a larger pipeline that will produce, years down the road, more forensic pathologists to meet the demand.

What to do? Well, as this issue evolves, week by week, stay in touch with your colleagues. Keep an eye on the listserv, one of the first places that new issues and challenges appear. Read and contribute to *Academic Forensic Pathology* – this is your journal and the voice of our profession. Come to NAME meetings – electronic communication is good, but face to face meetings are invaluable to both information exchange and networking. Spend some time informing your politicians, at every level; they are hungry for clearly-presented data and your voice of reason is invaluable to them. Most of all, please remain connected to, and involved with, NAME. We will get through this.

Letter From the Guest Editor

A handwritten signature in black ink that reads "Thomas P. Gilson MD".

Thomas P. Gilson MD
Guest Editor

I am honored to serve as guest editor for this issue of *AFP* devoted to the opioid crisis. The invited contributors, reviewers, Editor-in-Chief, and staff at *AFP* have my sincerest thanks for their efforts to get these papers written and submitted, reviewed, edited, and published. This topic is timely both on a public and professional level and the papers cover several areas relevant to the epidemic we are seeing unfold in communities around the nation.

The fundamental aspects of scene investigation are addressed as well as issues around postmortem examination, including the feasibility of compliance with our professional organization's recommendation to conduct full autopsy examinations on drug-related deaths. In many jurisdictions the opioid epidemic has exacerbated the shortcomings of death investigation in the United States both in areas of long-standing de-

ficiencies in adequately trained personnel and funding. The National Association of Medical Examiners has long emphasized the need for more forensic pathologists and the increased caseloads precipitated by the opioid crisis are driving this point home in many regions, where several offices now face challenges to maintain adequate staff for accreditation purposes and comply with best practices. These increased caseloads of course ripple into several other areas of forensic practice, most notably toxicology.

Medical examiners are a presence in both legal and public health systems and it is my hope that this issue of *AFP* addresses both dimensions. As prevention of drug-related deaths becomes an increasing focus of the general community, legal prosecutions have increased and medical testimony is expected. Understanding the legal standards for prosecution (and their



limitations) creates a climate in which both accountability and fairness can be achieved. Several articles are also devoted to attempts to work within the public health system to impact the drug problem, whether these include using tools like prescription monitoring programs to augment practice or tabulating and sharing data to bring emerging trends in these deaths to attention more rapidly than traditional aggregate death certificate data analysis.

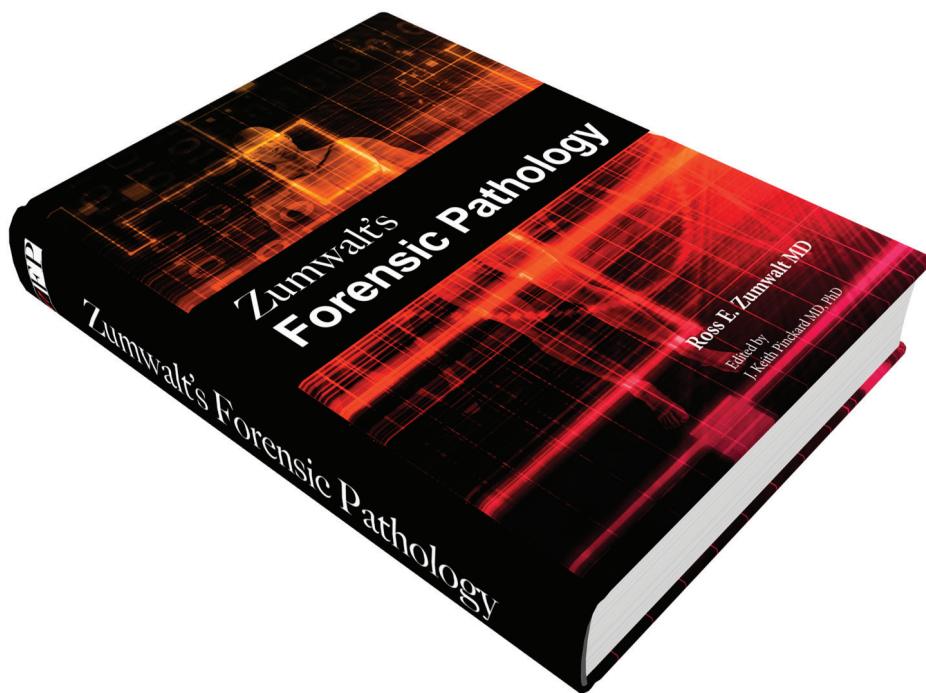
Drug overdose has been the most common form of accidental death for nearly a decade now (surpassing motor vehicle crashes). Tens of thousands of our fellow citizens are dying each year from drug overdoses and these deaths touch many families and friends of the decedents. Listening to the lessons these decedents have to teach is essential in our mission to serve the living.

Dr. Zumwalt practiced forensic pathology for 40 years — instead of practicing one year of forensic pathology 40 times...

A book about HOW and WHY we practice the way we do, and how to GROW as we practice...

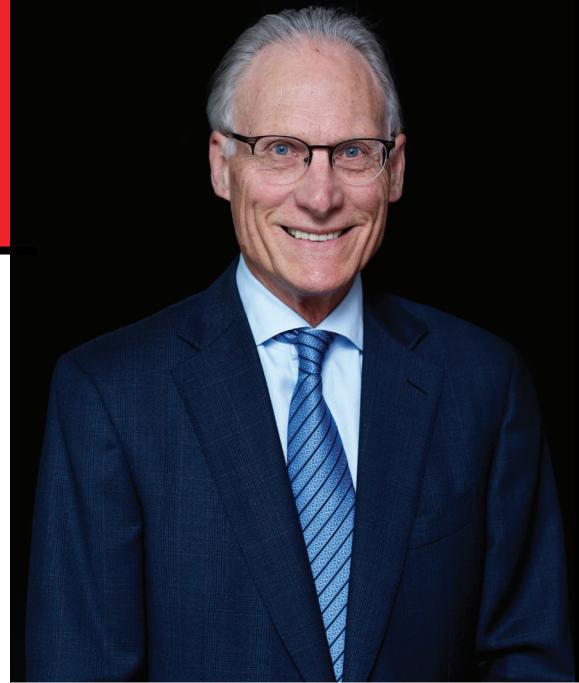
**PRE-ORDER BY MAY 31, 2017
TO SAVE \$100**

<https://store.academicfp.com>



Foreword by Randy Hanzlick MD

Published by Academic Forensic Pathology International



Ross Zumwalt MD

(Former) Chief Medical Investigator
New Mexico OMI

Zumwalt's Forensic Pathology includes:

- Death certification
- Death investigation
- The forensic autopsy
- Ancillary laboratory studies
- Apparently natural death
- Apparently accidental death
- Apparently suicidal death
- Apparently homicidal death
- Deaths whose manner cannot be determined
- Other topics

Approximately 500 pages

Published in brilliant full color

Estimated release: Fall 2017

Full retail price \$350 USD



SCHOLARLY CONTENT

Volume Seven Issue One March 2017



Drug Intoxication and the Need to Autopsy: A Diagnosis of Exclusion?

David R. Fowler

ABSTRACT

The recent surge in drug deaths has focused attention on the diagnosis of drug intoxication as a cause of death. In Maryland, the Department of Vital Records has shown an increase from 649 intoxication deaths in 2012 to 1259 in 2015. Preliminary data for 2016 document 1892 of these deaths. Many of the medicolegal death investigation offices in the United States are facing potential loss of accreditation. There is limited capacity to add more staff due to a lack of appropriately trained pathologists and budget constraints. The diagnosis of this intoxication and the need to autopsy all of these cases is a matter of debate, as many death investigation offices look for alternative means to maintain accreditation. The alternative to adding more staff is to reduce the autopsy caseload. Can this be done without compromising the intent of the medical examiner system and the law? Balancing this with being fiscally responsible may be a very real challenge and one that will test many death investigation systems due to this pandemic of drug deaths. If there is a need to reduce the autopsy caseload, it should be in cases other than where the diagnosis is one of exclusion. *Acad Forensic Pathol.* 2017 7(1): 2-6

AUTHORS

David R. Fowler MD, Maryland Office of the Chief Medical Examiner

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

CORRESPONDENCE

David R. Fowler MD, 900 W Baltimore St, Baltimore MD 21223, fowlerd@ocmemd.org

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Exclusion, Resources, Autopsy

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.001>

Submitted for consideration on 29 Dec 2016. Accepted for publication on 2 Feb 2017



INTRODUCTION

The recent surge in drug deaths has focused attention on the diagnosis of drug intoxication as a cause of death. In Maryland, the Department of Vital Records has shown an increase from 649 intoxication deaths in 2012 to 1259 in 2015 (1). The first two quarters of 2016 document 920 of these deaths (1) and show no abatement for this cause despite aggressive public health and law enforcement initiatives.

The diagnosis of this intoxication and the need to autopsy all of these cases is a matter of debate, as many death investigation offices look for alternative means to maintain accreditation. The alternative to adding more staff is to reduce the autopsy caseload. Can this be done without compromising the intent of the medical examiner system and the law? Balancing this with being fiscally responsible may be a very real challenge and one that will test many death investigation systems due to this pandemic of drug deaths. If there is a need to reduce the autopsy caseload, it should be in cases other than where the diagnosis is one of exclusion.

DISCUSSION

Public health and law enforcement initiatives have been put into place to mitigate this pandemic of drug-related deaths. One such initiative is the education of individuals (e.g., police, prehospital, lay persons) trained to administer naloxone under the overdose response program. To date, 39 083 personnel have received this training (2). These initiatives are reliant on accurate cause of death data to allow for planning and evaluation of the interventions.

At the level of death investigation, this surge in drug deaths has placed already strained death investigation systems in the United States in a precarious position. Many of the offices are facing potential loss of accreditation due to the maximum workload of each practicing pathologist being limited to a maximum of 325 autopsies each per year, with a recommended maximum of 250 (3, 4). For each additional 250 to 325 cases at an office, the institution should add a patholo-

gist. There is limited capacity to add more staff due to a lack of appropriately trained pathologists, facilities, and budget constraints.

In the case of the state of Maryland, the increased workload should result in the addition of four pathologists from 2012 to 2016. To further complicate this surge in intoxication deaths are the increased deaths occurring from other causes and manners. Some of these may well be related to violence often associated with the drug trade. Others may be unrelated and associated with other factors such as affordable gasoline and miles driven, creating additional motor vehicle casualties.

The diagnosis of this intoxication and the need to autopsy all of these cases is a matter of debate, as many death investigation offices look for alternative means to maintain accreditation. The alternative to adding more staff is to reduce the autopsy caseload. Can this be done without compromising the intent of the medical examiner system and the law?

Most statutes call for an investigation to determine the cause of death within a reasonable degree of medical certainty. That level of confidence is the subject of debate and many peer-reviewed publications (5, 6). To further compound this issue is the common use of statistics as a diagnostic tool in sudden death. Statistically, as the population ages, we have data that show an increase in natural deaths, such as cardiovascular disease. As medical examiners, we have used those data to provide a scientific argument for certifying sudden deaths under our jurisdiction without doing an autopsy. We also all recognize that those persons not autopsied, but certified as cardiovascular disease, then add to these data to further prove our so-called accurate scientific assumption.

Accurate death certification serves both the public's health and safety. Examples of processes served by a death certificate or an autopsy report are: new emerging threats to the public's health, the judicial process (both criminal and civil), the families' need to understand the death as part of bereavement, genetic counseling, estate resolution, and insurance claims. The



accuracy of death certification is significantly compromised if an autopsy is not performed (7).

So can we in good conscience ignore these needs and only test the blood for foreign substances and make a decision based on those results alone?

As this pandemic of drug deaths has evolved, we noticed at the Office of the Chief Medical Examiner for Maryland that the age group most affected is the 50- to 60-year-olds. This challenges our previous assumption that these sudden deaths were due to cardiovascular diseases. We have all pondered, or at least given some thought to the age-old concept of “a” cause of death versus “the” cause of death. This question cannot be answered without an autopsy in a case where the diagnosis is one of exclusion such as drug-related, sudden unexplained death in infancy, or drowning. Where can we reasonably turn to identify guidance on this issue?

The National Association of Medical Examiners (NAME) autopsy standards and the NAME checklist speak to this issue. In addition to the accreditation checklist (3), which is a product of the inspection committee and requires board approval, we have the autopsy performance standards. Arguably, as these are debated and approved by the membership, they are a more powerful statement of our professional standards.

Standard B3 provides guidelines as to which medico-legal death investigations need to have an autopsy as part of the process (4). Part of the preamble to the list of cases requiring autopsy states language similar to that used above.

Performing autopsies protects the public interest and provides the information necessary to address legal, public health, and public safety issues in each case (4).

There is language allowing discretion of the pathologist or local guidelines for autopsies on cases other than listed and indicates certain categories where the public’s interest is “so compelling” that an autopsy

should be performed. Item B3.7 is “*apparent intoxication by drugs, alcohol or poison.*” One other category listed is suspected drowning (4).

We can also add sudden death in infancy as a critical category as well. While the use of sudden infant death syndrome as a cause of death is becoming less popular, the definition specifically made this a diagnosis of exclusion. Any case where the cause of death is one arrived at as a process of exclusion mandates the need for an autopsy.

The National Association of Medical Examiners also has another substantial, grass roots type resource. Position papers have a period where the membership may comment, and the Board of Directors must approve the draft. One such article that was authored recently and is still in effect is the one on opioid-related deaths. In this paper, Davis et al. specifically stated that: “*an autopsy provides the most accurate means of determining the cause of death*” (8). Further, the authors indicated that a medical examiner or coroner (ME/C) assume jurisdiction and perform an autopsy to determine the cause and manner of death whenever intoxication is suspected as a possible cause of death (8).

The investigation of the scene of death is as critical a part of the decision-making process and is the subject of another paper in this issue (9).

The facts surrounding the use of these often illicit substances are sometimes occult, and the fact that a third party often provides the history, can complicate our responsibilities. Even in cases with a previous history of use of drugs, we do not have the level of detail we need. What substance(s), source, how often, what dose, and over what period, are questions to which we often do not get appropriate answers. These speak to risk, tolerance, metabolic capacity, and pharmacological interactions. How many die during their first experiment with these substances, or have they been using these substances for years? Now that we are seeing an increased number of older users, it may speak to years of use, at least intermittently, although one cannot exclude a person over 50 years of age having the first exposure to a drug.

The use of statistics and a cutoff age in a decision matrix, allowing a presumption that these deaths are cardiovascular, collides with this new data on the use of drugs in the older age groups. If the scene does not have any indication of drug use and there is no history of such use forthcoming, we could easily improperly certify the death as a natural. Similarly, if we do not autopsy and miss significant disease or occult trauma and rely on the toxicology results, we also generate false results. These false negatives and false positives hurt our communities and are contrary to our governing statutes.

Drug deaths could be considered an environment hazard to those exposed to them, especially, in this era of adulteration of the heroin supply with potent synthetic opioids. Not identifying these and warning the public health and law enforcement machines is similar to missing other environmental hazards (e.g., carbon monoxide death due to a faulty boiler).

Even the fastest forensic toxicology laboratory will not allow for results in advance of making a decision to autopsy. There have been attempts to use screening point of service kits, but many of these are too specific and will miss some of the new emerging substances.

From the aspect of community risk and burden, do we need to identify every case? Hospital pathologists are trained to sample a specimen and obtain representative sections to arrive at a diagnosis in the individual case or sample. Can we reasonably apply this to a community or a cohort of deaths? If we want to satisfy just the public health aspects of this problem to some degree and identify a trend, perhaps this would be acceptable. One will eventually determine the substance at some point, but what may have occurred in the interim, and at what cost to the community and the individuals?

In many situations, a death investigator will have to judge the value of various comorbidities. In the elderly population, we see coronary artery disease that has far exceeded our usual threshold of stenosis for a potential death. In that case, the person has been living with that for a considerable period. The same applies to a seizure disorder that has been present for years.

If we invoke that as the cause of death, we should be asking "why today and not before?" Many drug users have been ingesting the substances for considerable periods of time. Why did it kill today? Without an autopsy to identify comorbidities and their relative risk, we are guessing. In some cases, an apparent drug death may have no comorbidities and negative toxicology. Is that a case where a new substance that is not part of the usual panel detected by the laboratory or is it below the threshold of detection? The efficacy of some of the new synthetic opioids is such that they can kill at very low doses, close to or below the threshold of detection.

Looking at the level of a substance in the blood also can be problematic (8). False elevated or lowered drug levels due to postmortem redistribution are of concern (10). Some drugs are prone to postmortem elevation, and others can be falsely depressed. While postmortem redistribution must be considered, we also must look at the issue of agonal redistribution and the effects of resuscitation and a period of survival. In the event of a rapid injection of an opioid, the respiratory center function is impaired by the bolus. At the same time, the vascular function will continue unabated for a variable time, distributing the substance more widely with dilution and some will be distributed to some degree into other pharmacological compartments. Relying on postmortem blood levels can be very misleading for these reasons and will not substitute for an autopsy. An epidemiological study to look at the number of excess deaths we now have, over those expected if the adulteration of the drug supply had not occurred will provide some clarity in this area. This is the subject of an ongoing project at the Office of the Chief medical Examiner for Maryland.

CONCLUSION

Simply ignoring the accreditation and practice standard limits threatens the recruitment and retention of forensic pathologists. Now, more than at any other time, accurate certification of deaths from a cause that is a major threat to the public's health is critical. These data inform so many potential interventions and also act as an important tool in the evaluation of these in-

terventions. Not fully investigating these deaths with a full autopsy to properly evaluate them completely threatens the intent of a competent medicolegal death investigation system. At a time of crisis it is appropriate instead to increase the resources needed.

REFERENCES

- 1) Drug- and alcohol-related intoxication deaths in Maryland. Data update through 2nd quarter 2016 [Internet]. Baltimore: Maryland Department of Health & Mental Hygiene; 2016 [cited 2016 Dec 29]. 14 p. Available from: [http://bha.dhmh.maryland.gov/OVERDOSE_PREVENTION/SiteAssets/Pages/Data-and-Reports/Quarterly%20report_2nd%20quarter%202016%20\(1\).pdf](http://bha.dhmh.maryland.gov/OVERDOSE_PREVENTION/SiteAssets/Pages/Data-and-Reports/Quarterly%20report_2nd%20quarter%202016%20(1).pdf).
- 2) The overdose response program [Internet]. Baltimore: Maryland Department of Health & Mental Hygiene; 2016 [cited 2016 Dec 29]. Available from: <http://bha.dhmh.maryland.gov/NALOXONE/Pages/Home.aspx>.
- 3) NAME inspection and accreditation checklist [Internet]. Walnut Shade (MO): National Association of Medical Examiners; 2014 Feb [cited 2016 Dec 29]. 32 p. Available from: https://netforum.avectra.com/Public/DocumentGenerate.aspx?wbn_key=1c456df3-47c6-4805-a3cf-9971eeb78d2f&SITE=NAME.
- 4) Forensic autopsy performance standards [Internet]. Walnut Shade (MO): National Association of Medical Examiners; 2016 Sep [cited 2016 Dec 29]. 26 p. Available from: https://netforum.avectra.com/Public/DocumentGenerate.aspx?wbn_key=684b2442-ae68-4e64-9ecc-015f8d0f849e&SITE=NAME.
- 5) Dias MS, Boehmer S, Johnston-Walsh L, Levi BH. Defining 'reasonable medical certainty' in court: what does it mean to medical experts in child abuse cases? *Child Abuse Negl.* 2015 Dec; 50: 218-27. PMID: 26589362. <https://dx.doi.org/10.1016/j.chab.2015.10.027>.
- 6) Drogin EY, Commons ML, Gutheil TG, et al. "Certainty" and expert mental health opinions in legal proceedings. *Int J Law Psychiatry.* 2012 Sep-Dec; 35(5-6):348-53. PMID: 23022469. <https://dx.doi.org/10.1016/j.ijlp.2012.09.002>.
- 7) Nashelsky MB, Lawrence CH. Accuracy of cause of death determination without forensic autopsy examination. *Am J Forensic Med Pathol.* 2003 Dec; 24(4):313-9. PMID: 14634467. <https://dx.doi.org/10.1097/01.paf.0000097857.50734.c3>.
- 8) Davis GG; National Association of Medical Examiners and American College of Medical Toxicology Expert Panel on Evaluating and Reporting Opioid Deaths. National Association of Medical Examiners position paper: recommendations for the investigation, diagnosis, and certification of deaths related to opioid drugs. *Acad Forensic Pathol.* 2013 Mar; 3(1):77-83. <https://doi.org/10.23907/2013.011>.
- 9) Morgan D. Opioid drug death investigations. *Acad Forensic Pathol.* 2017 Mar; 7(1):50-59. <https://doi.org/10.23907/2017.006>.
- 10) Pounder DJ, Jones GR. Post-mortem drug redistribution—a toxicological nightmare. *Forensic Sci Int.* 1990 Apr; 45(3):253-63. PMID: 2361648. [https://doi.org/10.1016/0379-0738\(90\)90182-x](https://doi.org/10.1016/0379-0738(90)90182-x).



Confronting an Upsurge in Opiate Deaths With Limited Resources

Thomas A. Andrew, Jennie V. Duval

ABSTRACT

The dramatic increase in drug-related deaths in the last decade has presented fiduciary and logistical difficulties to medicolegal jurisdictions of all types and sizes. New Hampshire, with a centralized state medical examiner system of death investigation, has been confronted with the task of investigating these drug-related deaths against the backdrop of statutory hurdles inhibiting a nimble response to the situation. This has led to a collaborative approach with law enforcement and the state Department of Justice in terms of triaging drug deaths to full autopsy versus external examination with toxicology testing. Preliminary data suggest that between 11 and 13% of suspected drug deaths have an alternative cause of death revealed by autopsy. Positive toxicological findings were documented in 97.5% of cases in which only an external examination was performed; however, some of these cases may have had undetected, significant internal findings that could have accounted for an alternative cause of death if an autopsy had been performed. While the case triage system described has temporarily addressed the acute problem, the issue of the medical examiner's appropriate role in the adequate evaluation of public health and safety remains extant. Furthermore, noncompliance with the National Association of Medical Examiners inspection and accreditation standards puts this agency, and others facing the same issues, at risk of losing full accreditation status until such resource issues are addressed by legislators and other stakeholders in the quality of medicolegal death investigation in the United States. *Acad Forensic Pathol.* 2017 7(1): 7-18

AUTHORS

Thomas A. Andrew MD, Office of Chief Medical Examiner, State of New Hampshire

Roles: A – Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

Jennie V. Duval MD, Office of Chief Medical Examiner, State of New Hampshire

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

CORRESPONDENCE

Thomas A. Andrew MD, 246 Pleasant Street Suite 218, Concord NH 03301, TAndrewME@comcast.net

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Opiates, Fentanyl, Autopsy, Scene investigation

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.002>

Submitted for consideration on 14 Dec 2016. Accepted for publication on 3 Jan 2017

INTRODUCTION

The last two decades have seen drug-related deaths increase by an order of magnitude in the state of New Hampshire (**Figure 1**). The upswing has been particularly swift in the last four years. In the late 1990s, there were 30-40 drug deaths annually in the Granite State. The mid 2000s saw major increases in prescription opiate/opioid abuse, with deaths approaching 200 per year and methadone being the agent most commonly indicated (**Figure 2**). The reemergence of heroin as a leading cause of drug-related fatalities in 2011 and recent emergence of illicit fentanyl and its analogues have pushed drug deaths to unprecedented levels (**Figure 3**). To date, fentanyl analogs isolated in our case material include U-47700, furanylfentanyl, acetylentanyl, and fluorofentanyl.

Current intelligence suggests that fentanyl analogs are illicitly produced by clandestine laboratories, likely in Mexico and/or China, which then utilize the preexisting heroin distribution infrastructure to disseminate the drug. Contraband may appear as a pure

white, light tan, or light brown powder, and range from fine to coarse to cake-like and crumbly, resembling powdered milk. The brown color comes from lactose that has been heated and caramelized slightly. Some packets will have a medicinal or chemical odor, but this is not characteristic. The product is typically sold like heroin in small ziplock-type plastic bags and bindles. There have been recent seizures in this jurisdiction and elsewhere of synthetic fentanyl pressed into tablets masquerading as hydrocodone and oxycodone. **Image 1** shows a 40 mg oxycodone pill side-by-side with pills seized in this jurisdiction, which, on analysis, were found to contain pure fentanyl.

At the time of this writing, it is projected that drug fatalities will number 488 by the end of the calendar year. Deaths are seen in decedents of a wide age range (**Figure 4**) and, like most high risk behaviors, tend to involve males two to three times more often than females (**Figure 5**). The decided majority of drug intoxications are certified as accidents (**Figure 6**). In 2014, the last for which nationwide data is available, New Hampshire, with its population of 1.33 million, ranked

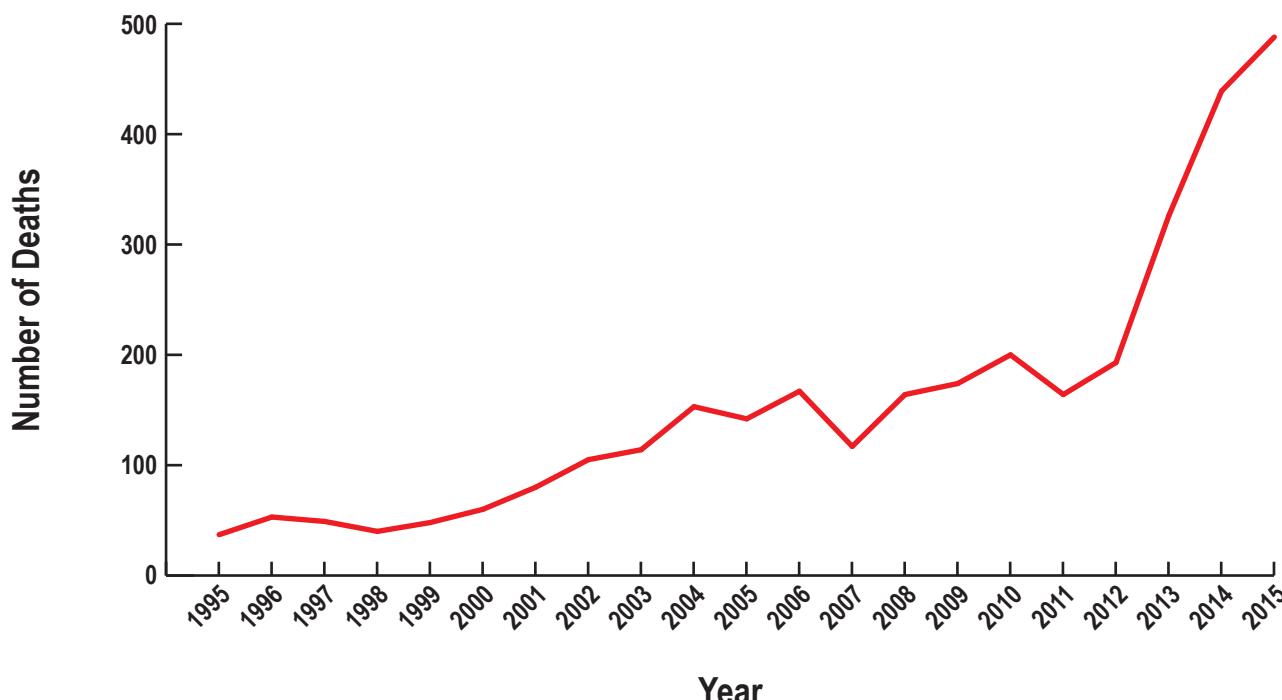


Figure 1: New Hampshire drug deaths, 1996-2015.

third in the United States, with 26.2 drug deaths per 100 000 population (1).

Ripple effects of these trends can be seen in other areas that directly impact the death investigation system in New Hampshire. After nearly a decade of slow but steady decline, traffic fatalities have increased from 95 in 2014, to 114 in 2015, and a projected 135 in 2016 (**Figure 7**). Suicides and homicides, which have remained flat for a decade, appear poised to increase as well. In addition, the potential for workplace exposure to hepatitis C has dramatically increased. All these developments are against a background of a medical examiner statute (2) that establishes two forensic pathologist positions and no provision for building any “surge capacity” to meet a public health and safety emergency such as the current drug death situation. As

early as 2006, the State of New Hampshire Office of the Chief Medical Examiner (OCME) recognized the growing need for additional forensic pathology full-time equivalents, but in a climate of fiscal austerity, could not convince stakeholders this was a priority item compared to other needs deemed more pressing.

With drug deaths alone approaching 500, the remainder of OCME’s caseload, crippled toxicology and body transport budgets, and the prospect of no additional forensic pathologists to perform the extra autopsies, the situation was deemed unsustainable. An infusion of federal dollars directed at the problem did not translate into assistance for OCME, but did lead to the addition of two new prosecutors and the formation of a statewide Drug Death Task Force (DDTF) based in the Department of Justice (DOJ). The mission of

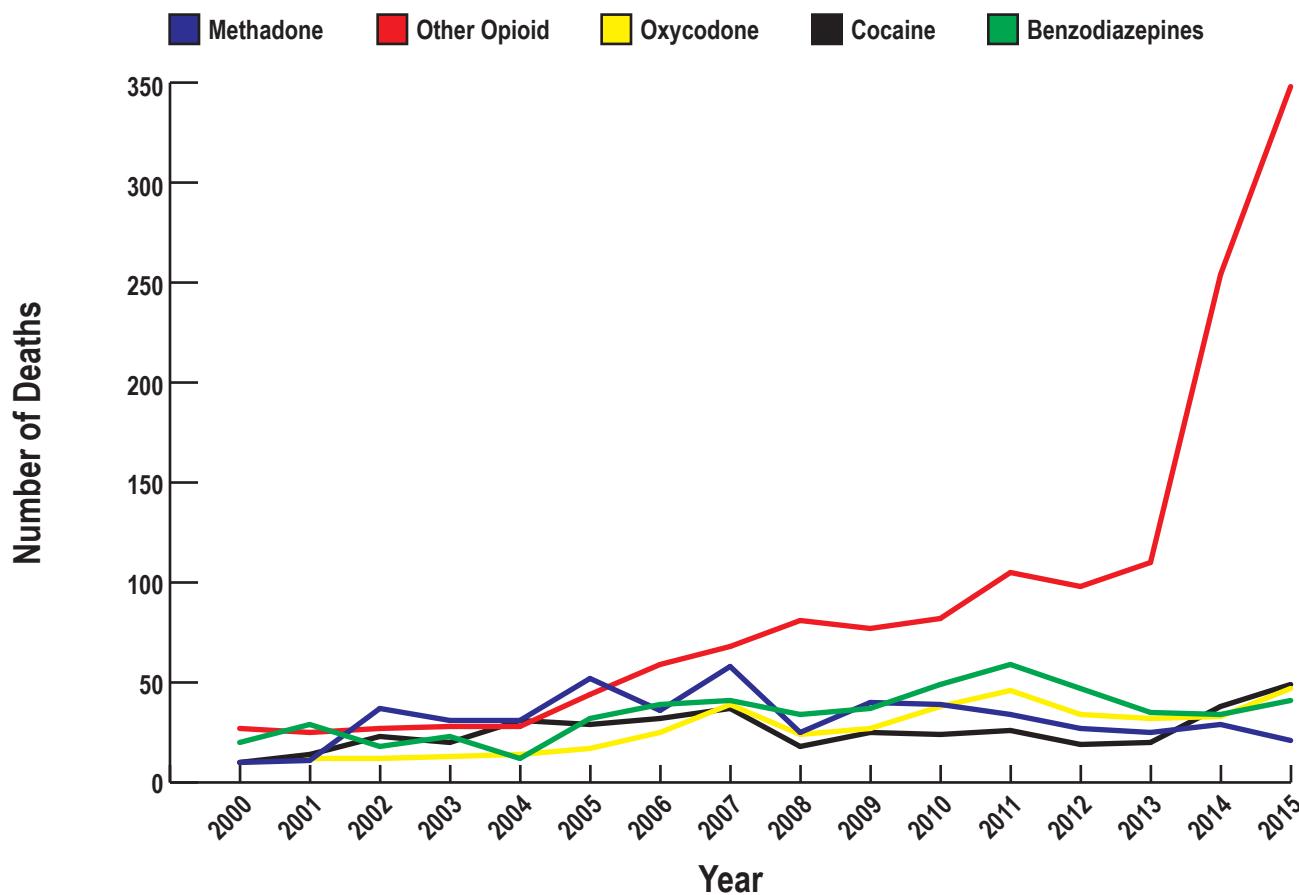


Figure 2: Drugs most commonly listed in death certificates, 2000-2015.

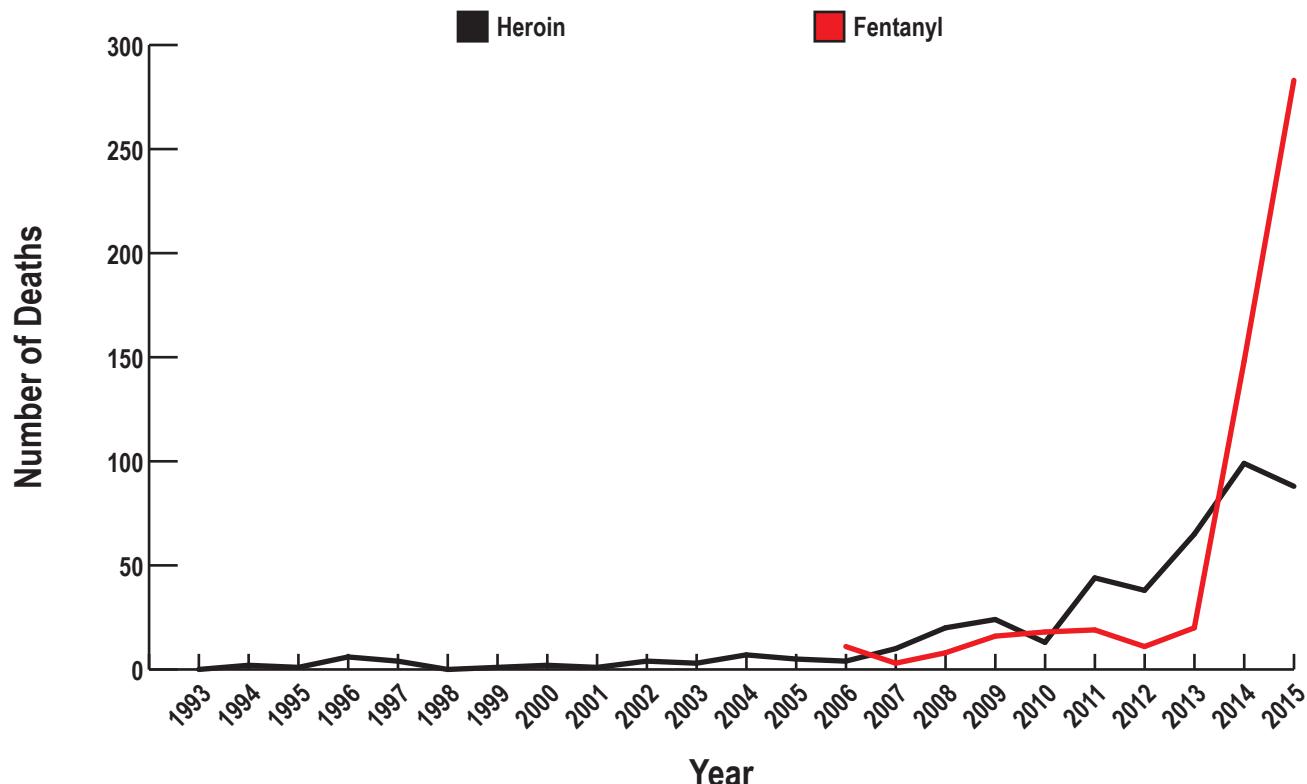


Figure 3: Emergence of heroin and fentanyl.



Image 1: Fentanyl marketed as oxycodone. A) Pharmaceutical oxycodone 40 mg. B) Seized by New Hampton, New Hampshire Police Department: pure fentanyl and no oxycodone.

the DDTF is ostensibly to more aggressively pursue prosecutions in drug deaths utilizing a “death resulting from” statute. This, of course, did not address the resource issue at OCME and negotiations commenced to find a middle ground.

The agreed upon protocol consists of a two-tiered approach to deaths that appear to be due to drug intoxication (**Figure 8**). For deaths occurring in hospitals, if there is a significant (days) survival interval and fatal intoxication has been proven or if the death is in the emergency department and no substantial case leads are developed within 24 hours, the case is released after external examination and procurement of appropriate toxicology specimens. If there is a survival interval but intoxication remains unproven or if the

death is in the emergency department and substantial case leads are developed within 24 hours, an autopsy is performed. Note that these decisions do not rely on emergency department or hospital drug screens. Routine toxicology testing in hospitals in our jurisdiction is typically performed on urine and will not detect fentanyl or fentanyl analogues. Positive results in urine may indicate recent use but not necessarily acute intoxication. Negative results will not rule out use of fentanyl and fentanyl analogues. In these cases, admission blood is obtained and submitted to a full service laboratory for comprehensive toxicology testing. With regard to scene deaths, the presence of drug paraphernalia, physical stigmata of recent drug use, known history of drug abuse, or witnessed event will result in external examination with toxicology unless

there are substantial case leads developed within 24 hours. In the latter case, as well as cases in which scene and circumstances are unclear, an autopsy is performed. A representative of the DDTK is on call 24 hours a day to “start the clock” on the development of case leads. The Office of Chief Medical Examiner, in cooperation with local funeral homes, will hold decedents for the 24 hour period within which case disposition is ultimately made.

Conspicuously absent in the system is input from the Public Health department. This is due, in part, to OCME being part of the DOJ in this jurisdiction. The unfortunate reality is that the Public Health department is also operating beyond capacity, and has raised no substantive objections to this approach. Neverthe-

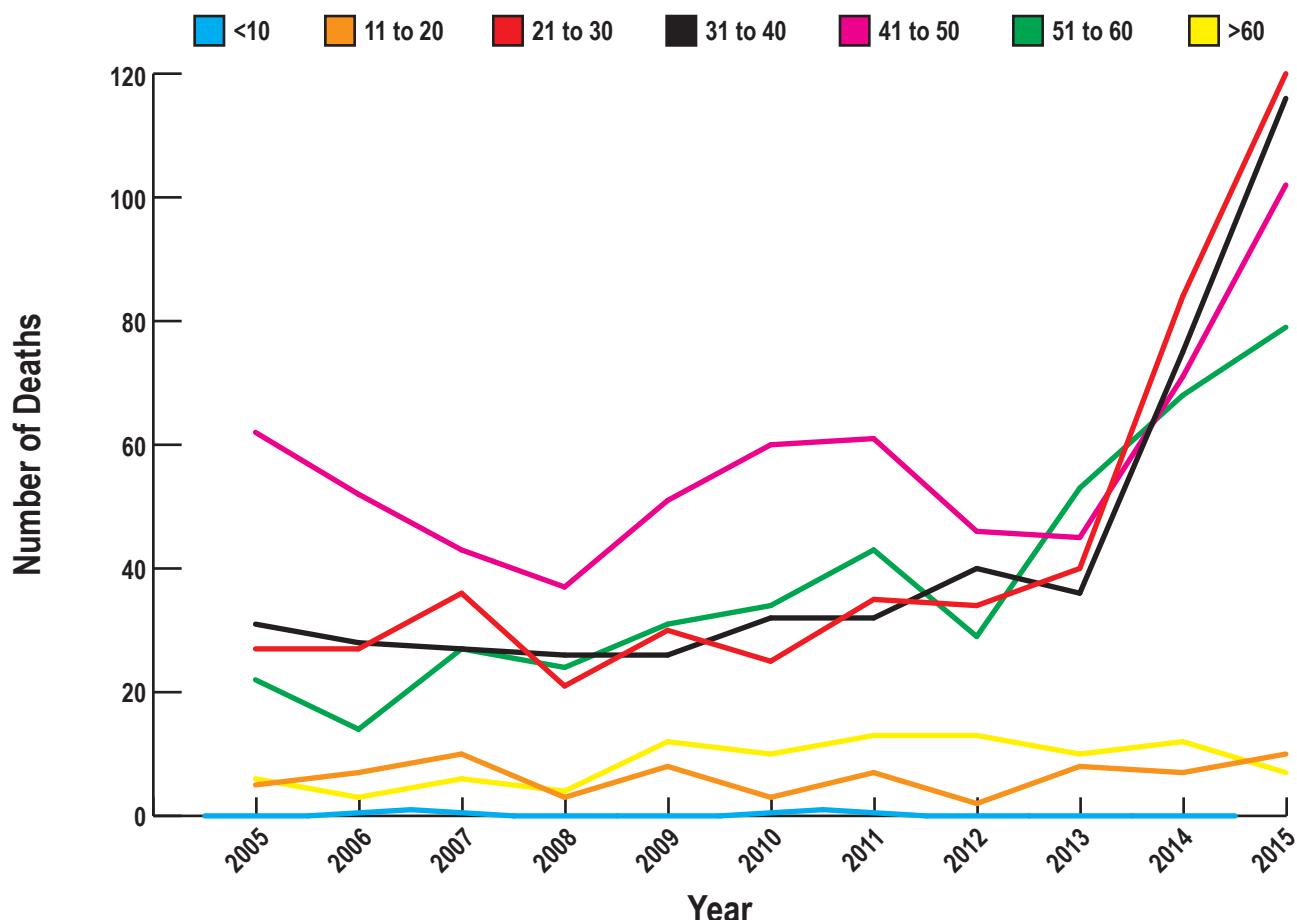


Figure 4: Drug deaths by age, 2005-2015.

less, there is public health impact addressed in our discussion. Undisputed is the existence of a National Association of Medical Examiners (NAME) autopsy performance standard to autopsy all suspected drug intoxication deaths (3). There are certainly medicolegal jurisdictions that have the capacity to absorb the extra caseload, but the reality in a jurisdiction with limited resources is that compliance with this standard will necessarily require noncompliance with other standards, including autopsies per pathologist, turn-around time parameters, and overall quality of work product.

Over many decades, there have been numerous studies documenting the inaccuracy of death certification without the benefit of autopsy (4-13). Discrepancy rates ranging from 9 to 40% have been identified in these studies, nearly all of which deal with inaccu-

racies of clinical diagnoses when compared to post-mortem examination. Four studies, one by Asneas and Paaske in 1980 (14), a second by Vanatta and Petty in 1987 (15), a third by Nashelsky and Lawrence in 2003 (16), and the fourth by Gill and Scordi-Bello in 2010 (17) specifically compared autopsy to external examination. The most common cause of death in these studies was some variation of hypertensive and arteriosclerotic cardiovascular disease. In the Nashelsky study, there were four fatal drug intoxications comprising 1.5% of the study group (16). No study specifically addressed the reliability of predicting fatal drug intoxication based on scene investigation, external examination, and toxicological analysis. The small, in-house study outlined below represents an effort to determine the reliability of this approach in the accurate determination of cause of death.

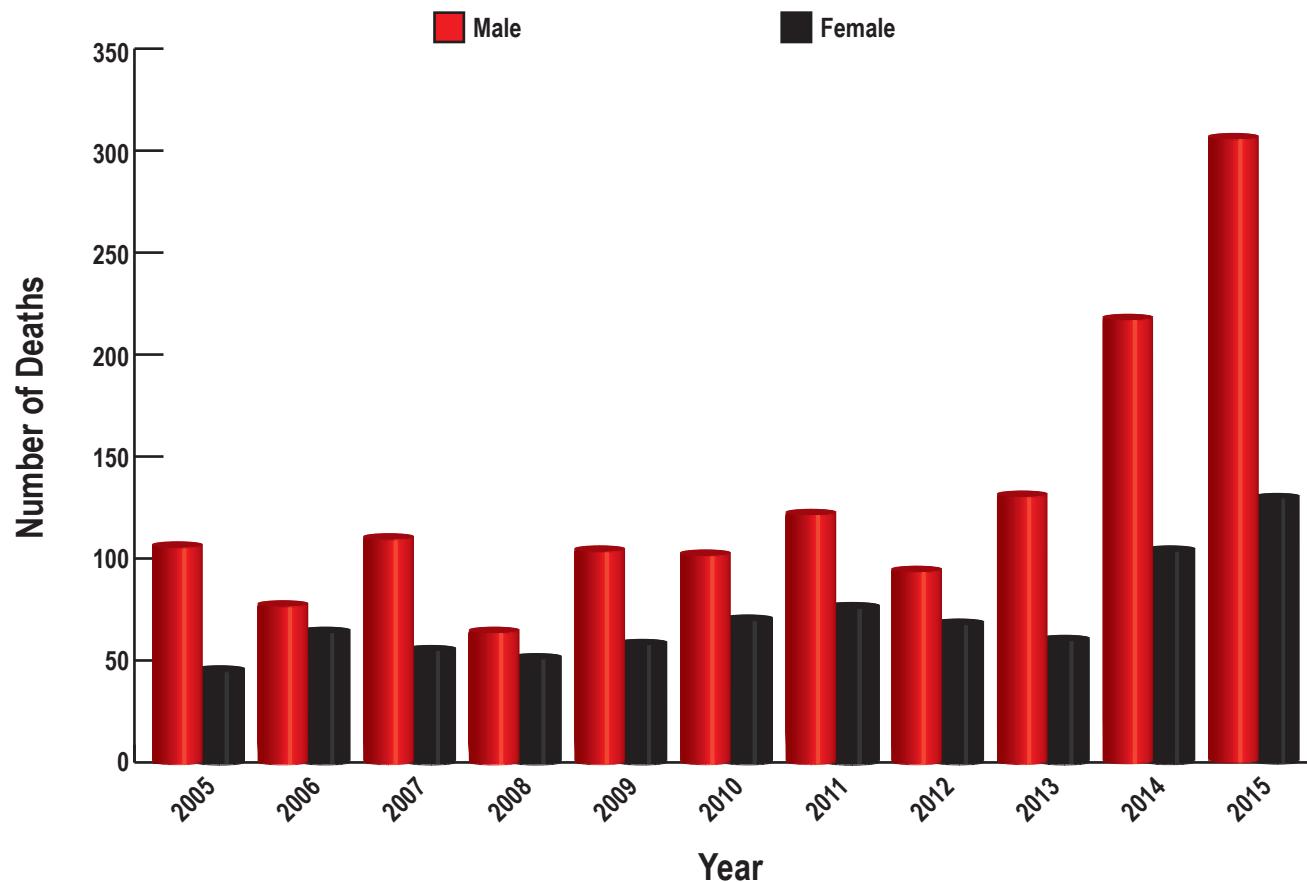


Figure 5: Drug deaths by sex, 2005-2015.

METHODS

Medical examiner cases flagged at initial investigation as likely drug-related were culled from OCME case management software. Ultimate cause of death for all such cases, both those autopsied and those released after external examination and procurement of toxicology specimens, were recorded. A comparison was then made between the two groups to determine what percentage of autopsy cases had causes of death other than drug intoxication versus what percentage of externally examined cases had nondiagnostic toxicology results. A retrospective review was then undertaken for calendar year 2010, at which time all suspected drug deaths were routinely autopsied.

RESULTS

To date in calendar year 2016, there have been 364 cases that have fallen into one or the other of the categories described above. Eleven cases remain pending

as of this writing and are not included in the statistics. Data are summarized in **Table 1**.

In 16 of 152 (10.5%) autopsied cases, an alternative cause of death was revealed. Eight were due to hypertensive and/or arteriosclerotic cardiovascular disease, three were due to acute ethanol intoxication, two were due to complications of chronic alcoholism, and two deaths were due to infections, one with acute bronchopneumonia and subacute myocarditis and another with sepsis with multi-organ system involvement in a person with AIDS. The last case involved a 36-year-old male with a long-standing substance abuse history found submerged near the bank of a river. Toxicology revealed ethanol concentration of 389 mg/dL and no other substances. Death was certified as due to drowning.

In five of 200 (2.5%) external-exam-only cases, an alternative cause of death was revealed, four of which were attributed to arteriosclerotic cardiovascular disease based on clinical history. The fifth case was an

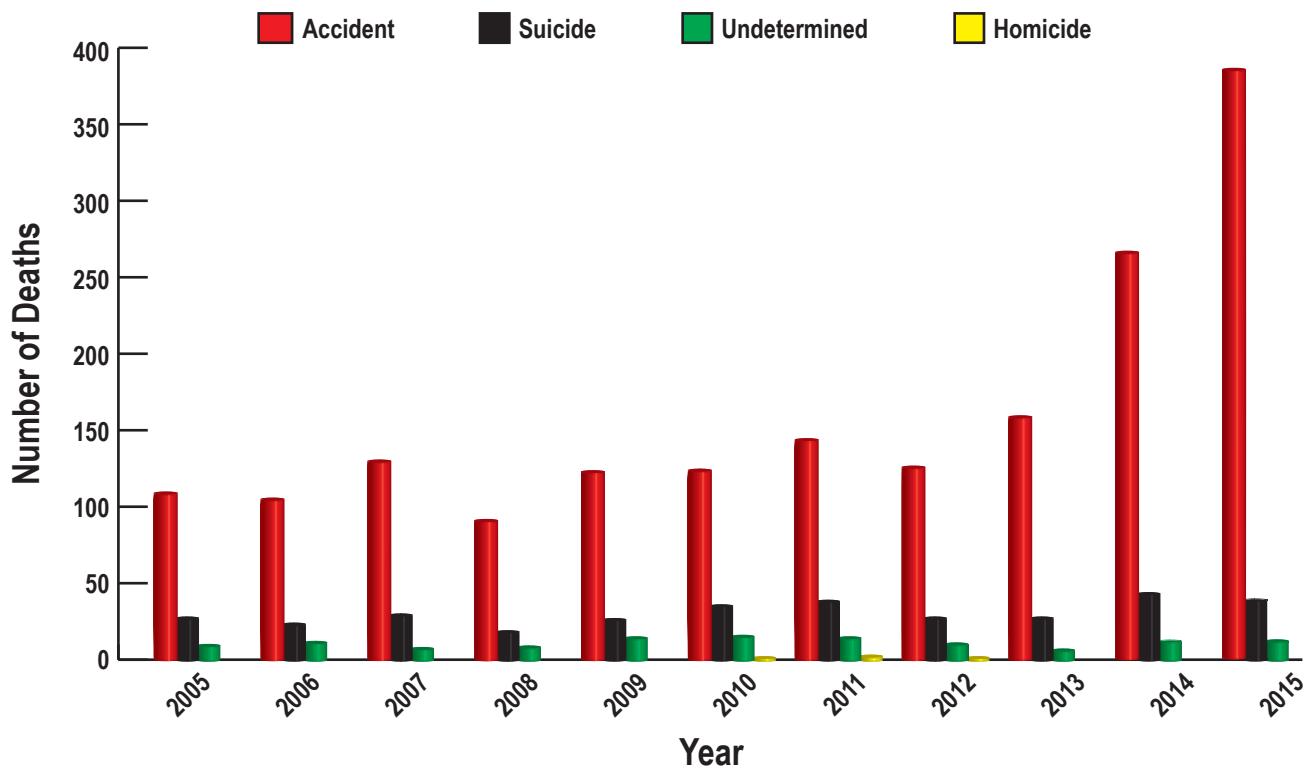


Figure 6: Drug deaths by manner.

individual with a documented intracerebral hemorrhage in which stimulant abuse was suspected, but not proven.

The 2010 data are summarized in **Table 2**. All 91 deaths suspected to be drug-related based on investigative information alone, were referred for autopsy. These represent cases wherein an external examination with toxicology would be performed in 2016. In 79 cases, the cause of death was indeed due to acute drug intoxication. Alternative causes of death revealed at autopsy in 12 (13.2%) cases included five deaths due to arteriosclerotic cardiovascular disease, and one each of meningitis, pulmonary thromboembolism, pulmonary vascular disease stemming from injection of oral pharmaceuticals, aspiration pneumonitis, acute ethanol intoxication, and diabetic ketoacidosis. One case was certified as manner undetermined. Of the 12 cases that had alternative causes of death, five (5.5%) had a positive toxicology screen. Results for this group are summarized in **Table 3**.

DISCUSSION

The aim of this brief review was to determine the reliability of the approach of not performing autopsies in all suspected drug-related deaths. The following are possible outcomes and explanations using such an approach:

1. No autopsy/Toxicology negative:
 - a. True cause of death missed by not doing autopsy
 - b. True drug death but agent undetected
 - i. Fentanyl analogues or novel psychoactive substances beyond laboratory detection capacity
 - ii. Drug metabolized to undetectable levels
2. No autopsy/Toxicology positive:
 - a. True drug death
 - b. Not a drug death, true cause of death missed by not doing autopsy

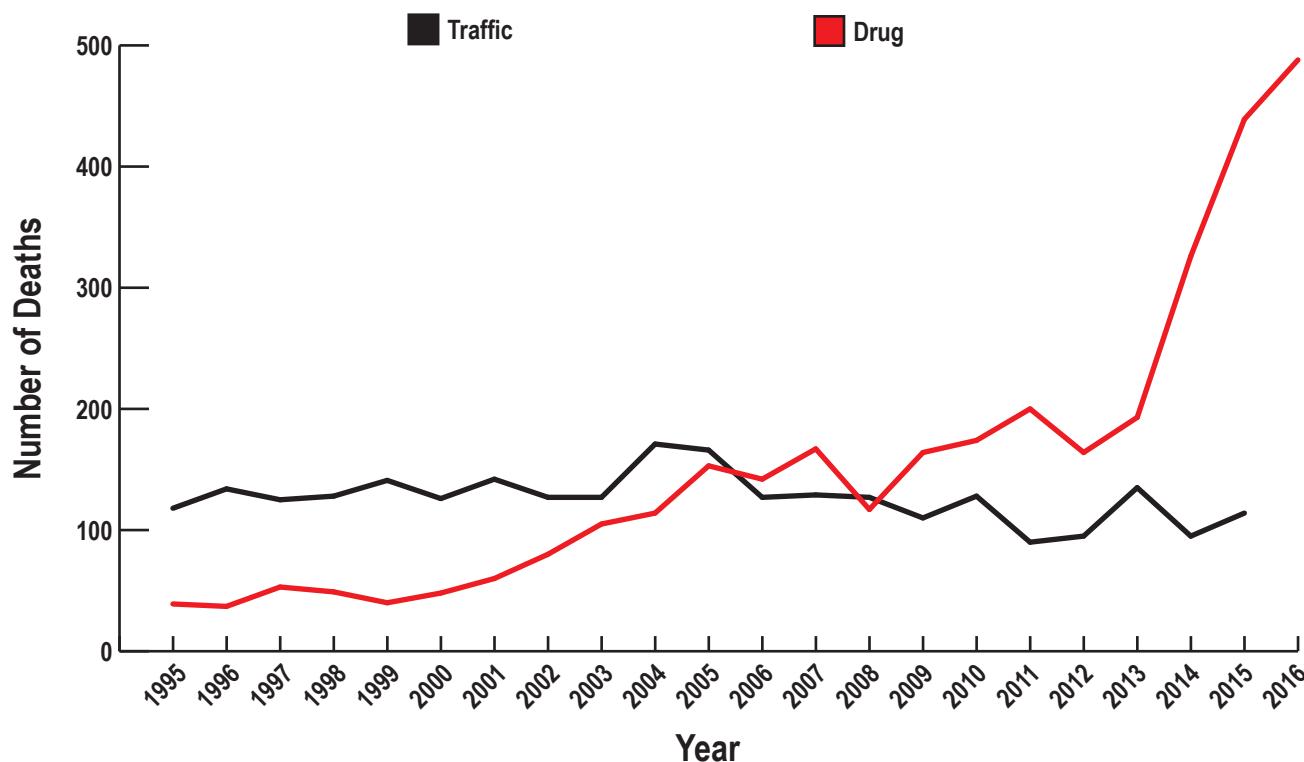


Figure 7: Drug deaths versus traffic deaths, 1995-2016.

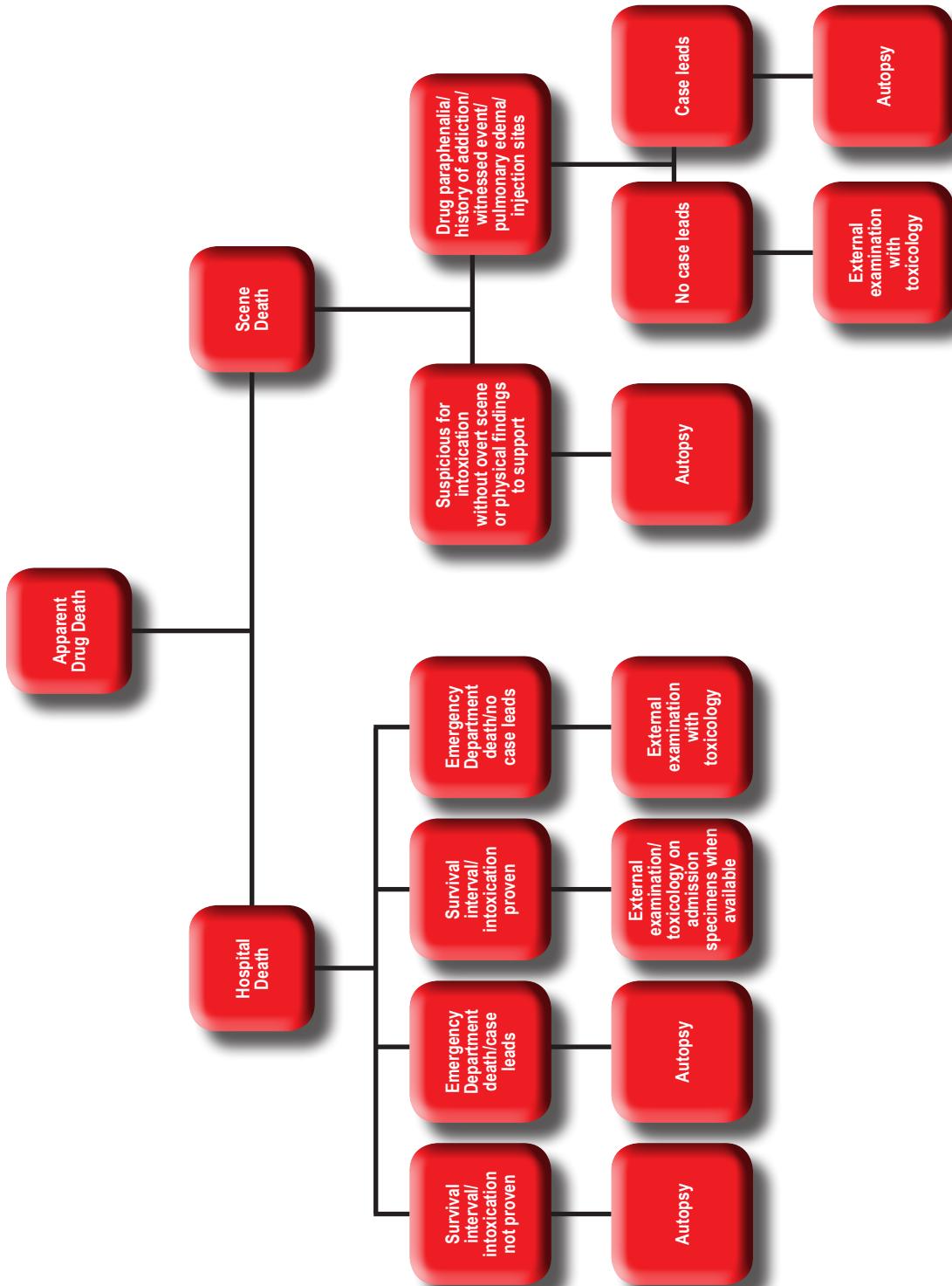


Figure 8: Case triage system for suspected drug deaths.

Page 15

Andrew & Duval • Limited Resources for Opiate Deaths
ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICOURNAL OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS
©2017 Academic Forensic Pathology International

Downloaded from www.afpjournal.com by an AFP Journal subscriber
This article is for personal use only and may not be shared or distributed in any fashion

The 10.5% rate of alternative causes of death in the autopsy group appears to be an endorsement of autopsying cases wherein, despite a known history or scene suggestion of drug intoxication, the circumstances of death remain murky. This also compares favorably with the 13.2% rate of alternative causes of death when all such cases were autopsied in 2010. None of the autopsy cases requested by law enforcement for prosecutorial purposes under the current system have had an alternative cause of death. If one is willing to assume the toxicology results in the 97.5% of exter-

nally examined subjects were sufficient to explain the deaths, this concordance rate appears satisfactory. However, as the 2010 data show, up to 5.5% of such cases may have been misclassified as drug deaths in absence of an autopsy. This can be extrapolated to a total of 12 of the 195 cases certified as drug deaths to have been misclassified. Answering the question of whether or not autopsying these individuals would have actually pushed the alternative diagnoses closer to the 10% of the autopsy group will require a differently designed study.

Table 1: Autopsy Versus External Only Examination, 2016

| N=352 | Autopsy (n=152) | External Examination (n=200) |
|--|-----------------|------------------------------|
| Toxicology sufficient to certify death due to intoxication | 136 (89.5%) | 195 (97.5%) |
| Toxicology not consistent with death due to acute intoxication | 16 (10.5%) | 5 (2.5%) |

Table 2: Autopsies of Suspected Drug Deaths, 2010

| N=91 | Autopsy of Suspected Drug Death |
|--|---------------------------------|
| Toxicological cause of death/Toxicology positive | 79 (86.8%) |
| Toxicological cause of death/Toxicology negative | 0 |
| Alternative cause of death/Toxicology positive | 5 (5.5%) |
| Alternative cause of death/Toxicology negative | 7 (7.7%) |

Table 3: Suspected Drug Deaths with Alternative Cause of Death and Positive Toxicology Screen, 2010

| Cause of Death | Postmortem Toxicology |
|---|--|
| Arteriosclerotic cardiovascular disease | Methadone 62 ng/mL Oxycodone 420 ng/mL |
| Acute and chronic pulmonary vascular disease with pulmonary hypertension from injection of oral pharmaceuticals | Amlodipine 60 ng/mL Acetaminophen 20 µg/mL Oxycodone 210 ng/mL Bupropion 130 ng/mL Hydroxybupropion 370 ng/mL Citalopram/Escitalopram 190 ng/mL |
| Arteriosclerotic cardiovascular disease | Methadone 720 ng/mL 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine 160 ng/mL Benzoylcegonine 240 ng/mL Hydroxyzine 20 mg/mL |
| Arteriosclerotic cardiovascular disease | Clonazepam 15 ng/mL 7-Amino Clonazepam 180 ng/mL Morphine 10 ng/mL Hydromorphone 18 ng/mL Nortriptyline 130 ng/mL Fluoxetine 140 ng/mL Norfluoxetine 190 ng/mL 6-Monoacetylmorphine 110 ng/mL (Urine) |
| Pulmonary thromboembolism due to obesity (Body mass index 41.4 kg/m ²) | Quetiapine 21 ng/mL Sertraline 51 ng/mL Buprenorphine 1.7 ng/mL Norbuprenorphine 1.7 ng/mL |

There are other alarming issues that spotlight the vulnerability of this case triage approach to error. For example, there were an additional 54 cases not suspected to be toxicologically mediated deaths at initial investigation that turned out to be drug intoxications, typically older individuals signed out as natural deaths with subsequent toxicology results that warranted an amendment of the original death certificate. Clearly, there is an unavoidable subjective component to the scene investigation that can influence the decision to bring in any given case for autopsy. The following examples were autopsied on the basis of a slightly atypical presentation for a drug-related death. Ideally, these individuals would have been autopsied under the guidelines in the flow chart above; however, some practitioners may have elected to only perform external examinations with toxicology, which may have led to erroneous death certification.

Case 1: 29-year-old female with a history of asthma, chronic pain and prescription drug abuse. Scene investigation revealed numerous unaccounted for oxycodone and alprazolam tablets. She became unresponsive while attempting nebulizer treatment. Autopsy findings were consistent with severe asthma. Postmortem toxicology showed free morphine, 6-monoacetylmorphine, and oxycodone.

Case 2: 41-year-old male with a history of intravenous drug abuse, found dead in the attic of a known “heroin house” with drug paraphernalia. There were recent complaints of fever and diarrhea. Autopsy revealed *Staphylococcus aureus* sepsis in the setting of acute influenza A infection. Fentanyl was detected in urine only.

Case 3: 24-year-old male with a history of insulin dependent diabetes mellitus and substance abuse found dead on bedroom floor with illicitly obtained buprenorphine nearby. There were recent complaints of vomiting. Autopsy revealed diffuse esophageal necrosis (“black esophagus”) and diabetic ketoacidosis. Postmortem toxicology showed a fentanyl concentration of 0.83 ng/mL.

Case 4: 27-year-old female with a history of heroin use arrested in the emergency department after presenting with altered mental status. The decedent’s sister offered a recent history of shortness of breath and lethargy. At autopsy there was necrotizing pneumonia and infective endocarditis. Postmortem toxicology showed a fentanyl concentration of 29 ng/mL.

Case 5: 30-year-old male with a history of substance abuse found gasping and moaning in bed following an apparent seizure. A spoon bearing powdery residue was in a pocket. Florid lyme carditis in a 704 g heart was the critical autopsy finding. Postmortem toxicology showed a fentanyl concentration of 7 ng/mL.

Case 6: 29-year-old male with a history of heroin use arrested for driving under the influence. He was driven home from jail by his wife and en route complained of sweating, nausea, vomiting. He was found dead in his bathroom hours later with a drug packet in his wallet. At autopsy, there was an occlusive thrombus in the left main coronary artery. Postmortem toxicology showed a fentanyl concentration of 5.4 ng/mL.

CONCLUSION

A case triage system developed to cope with a dramatically increased caseload stemming from this jurisdiction’s current struggle with opiate- and opioid-related fatalities has been presented. The retrospective data from 2010 to 2016 show a relatively high degree of reliability of this case triage method. We cannot, however, endorse such an approach over the long term. This preliminary study suggests that up to 5.5% of nonautopsy cases would be misclassified as drug intoxications and, as the individual cases outlined in the discussion section show, toxicological evidence in cases undergoing external examination only may suggest a drug-related death when autopsy would reveal an alternative, nontoxicological cause of death.

This goes beyond mere academic interest, as the current wave of opioid fatalities is an important public health issue, and when these deaths involve the criminal justice system it is even more important to be correct. Both the public health and criminal justice



systems are not optimally served by this approach. Considering the latter, by convention, the death certificate standard is “more probable than not.” Our data suggest that 5.5% of cases not autopsied may be incorrectly certified as drug-related deaths. Is a 94.5% chance of being correct beyond a reasonable doubt? Regarding public health, missed alternative causes of death would not be recorded in vital statistics. In addition, OCME typically tests for hepatitis B, C and HIV in autopsy drug deaths but not on external examinations, save for the instance of a needle stick or other exposure.

While we unreservedly endorse the existing NAME standard of autopsying such cases, we remain firmly entrenched in a system that demands doing more for less. To date, we have not experienced any pushback from families given the potential delay in release of remains, though funeral homes have balked at being reimbursed for transport to OCME but not for transport to the holding funeral home from the scene of death. Additionally, more detailed study may further refine and improve the reliability of such a case triage system in the event that an office should remain under resourced, even in the face of a markedly increased caseload. Inaccurately classified cases could be examined in detail to develop improved case triage criteria. Some jurisdictions use commercially available field tests to determine disposition of such cases. Ideally, a study of autopsy results in cases that meet criteria for external examination as outlined in this preliminary study could be carried out to more directly assess the accuracy of the hypothesis behind the case triage system. Analysis of the cost benefit ratio as well as reliability of such an approach is worth further study as well. Analysis of the true cost of doing autopsies on all suspected drug deaths would describe in detail the actual financial burden of this approach in small, rural, or other under-resourced jurisdictions.

REFERENCES

- 1) CDC WONDER [Internet]. Atlanta: Centers for Disease Control and Prevention; 2015. Multiple cause of death 1999-2014; [cited 2016 Dec 14]. Available from: <https://wonder.cdc.gov/mcd.html>.
- 2) New Hampshire revised statutes annotated [Internet]. Title LIX, Proceedings in criminal cases, Chapter 611-B:1-31, Office of chief medical examiner; [cited 2016 Dec 14]. Available from: <http://www.gencourt.state.nh.us/rsa/html/lx/611-b/611-b-mrg.htm>.
- 3) Forensic Autopsy Performance Standards [Internet]. Walnut Shade (MO): National Association of Medical Examiners; c2016. Standard B3.7, p. 9; [cited 2016 Dec 14]. Available from: <https://netforum.avectra.com/public/temp/ClientImages/NAME/684b2442-ae68-4e64-9ecc-015f8d0f849e.pdf>.
- 4) Kircher T, Nelson J, Burdo H. The autopsy as a measure of accuracy of the death certificate. *N Engl J Med.* 1985 Nov 14; 313(20):1263-9. PMID: 4058507. <https://doi.org/10.1056/nejm198511143132005>.
- 5) Maclaine GD, Macarthur EB, Heathcote CR. A comparison of death certificates and autopsies in the Australian Capital Territory. *Med J Aust.* 1992 Apr 6; 156(7):462-3, 466-8. PMID: 1556973.
- 6) McKelvie PA. Medical certification of causes of death in an Australian metropolitan hospital. Comparison with autopsy findings and a critical review. *Med J Aust.* 1993 Jun 21; 158(12):816-8, 820-1. PMID: 8326892.
- 7) Hill RB, Anderson RE. An autopsy-based quality assessment program for improvement of diagnostic accuracy. *Qual Assur Health Care.* 1993 Dec; 5(4):351-9. PMID: 8018895. <https://doi.org/10.1093/intqhc/5.4.351>.
- 8) Ermenc B. Discrepancies between clinical and post-mortem diagnoses of causes of death. *Med Sci Law.* 1999 Oct; 39(4):287-92. PMID: 10581907.
- 9) Sington JD, Cottrell BJ. Analysis of the sensitivity of death certificates in 440 hospital deaths: a comparison with necropsy findings. *J Clin Pathol.* 2002 Jul; 55(7):499-502. PMID: 12101193. <https://doi.org/10.1136/jcp.55.7.499>.
- 10) Pritt BS, Hardin NJ, Richmond JA, Shapiro SL. Death certification errors at an academic institution. *Arch Pathol Lab Med.* 2005 Nov; 129(11):1476-9. PMID: 16253030.
- 11) Ravakhah K. Death certificates are not reliable: revivification of the autopsy. *South Med J.* 2006 Jul; 99(7):728-33. <https://doi.org/10.1097/01.smj.0000224337.77074.57>.
- 12) Tavora F, Crowder C, Kutys R, Burke A. Discrepancies in initial death certificate diagnoses in sudden unexpected out-of-hospital deaths: the role of cardiovascular autopsy. *Cardiovasc Pathol.* 2008 May-Jun; 17(3):178-82. PMID: 18402800. <https://doi.org/10.1016/j.carpath.2007.07.010>.
- 13) Mieno MN, Tanaka N, Arai T, et al. Accuracy of death certificates and assessment of factors for misclassification of underlying cause of death. *J Epidemiol.* 2016; 26(4):191-8. PMID: 26639750. <https://doi.org/10.2188/jea.je20150010>.
- 14) Asneas, S, Paaske, F. Uncertainty of determining cause of death in medicolegal material without autopsy: an autopsy study. *Forensic Sci Int.* 1980; 15:103-114. PMID: 7358323. [https://doi.org/10.1016/0379-0738\(80\)90149-8](https://doi.org/10.1016/0379-0738(80)90149-8).
- 15) Vanatta PR, Petty CS. Limitations of the forensic external examination in determining the cause and manner of death. *Hum Pathol.* 1987 Feb; 18(2):170-4. PMID: 3804321. [https://doi.org/10.1016/s0046-8177\(87\)80335-0](https://doi.org/10.1016/s0046-8177(87)80335-0).
- 16) Nashelsky MB, Lawrence CH. Accuracy of cause of death determination without forensic autopsy examination. *Am J Forensic Med Pathol.* 2003 Dec; 24(4):313-9. PMID: 14634467. <https://doi.org/10.1097/01.paf.0000097857.50734.c3>.
- 17) Gill JR, Scordi-Bello IA. Natural, unexpected deaths: reliability of a presumptive diagnosis. *J Forensic Sci.* 2010; 55(1):77-81. PMID: 20002277. <https://doi.org/10.1111/j.1556-4029.2009.01227.x>.



Opioid Toxicity

David Dolinak

ABSTRACT

In recent years, there has been a substantial increase in opioid use and abuse, and in opioid-related fatal overdoses. The increase in opioid use has resulted at least in part from individuals transitioning from prescribed opioids to heroin and fentanyl, which can cause significant respiratory depression that can progress to apnea and death. Heroin and fentanyl may be used individually, together, or in combination with other substances such as ethanol, benzodiazepines, or other drugs that can have additional deleterious effects on respiration. Suspicion that a death is drug-related begins with the decedent's medical and social history, and scene investigation, where drugs and drug paraphernalia may be encountered, and examination of the decedent, which may reveal needle punctures and needle track marks. At autopsy, the most significant internal finding that is reflective of opioid toxicity is pulmonary edema and congestion, and frothy watery fluid is often present in the airways. Various medical ailments such as heart and lung disease and obesity may limit an individual's physiologic reserve, rendering them more susceptible to the toxic effects of opioids and other drugs. Although many opioids will be detected on routine toxicology testing, more specialized testing may be warranted for opioid analogs, or other uncommon, synthetic, or semisynthetic drugs. *Acad Forensic Pathol.* 2017 7(1): 19-35

AUTHOR

David Dolinak MD, Cuyahoga County Medical Examiner's Office

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, principal investigator of a related study listed in the citations, general supervision, general administrative support, writing assistance and/or technical editing.

CORRESPONDENCE

David Dolinak MD, 11001 Cedar Ave, Cleveland OH 44106, ddolinak@cuyahogacounty.us

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The author, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The author has indicated that he does not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Opioid, Opiate, Respiratory depression, Heroin, Fentanyl

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.003>

Submitted for consideration on 5 Jan 2017. Accepted for publication on 30 Jan 2017

INTRODUCTION

In recent years, there has been a substantial increase in opioid use and abuse, and in opioid-related fatal overdoses, due at least in part from individuals transitioning from prescribed opioids to cheaper, more accessible illicit heroin and fentanyl (1-13). The term “opiate” technically refers to wholly natural substances found in the resin of the opium poppy, such as morphine and codeine, that have affinity for the body’s opioid receptors. “Opioid” is a broader term, and includes opiates, semisynthetic derivatives of opiates, and synthetic compounds that bind to the body’s opioid receptors, causing similar clinical effects as opiates. Opioids, by acting on the opioid receptors, have the beneficial therapeutic effect of blocking pain sensation, but also may cause various deleterious effects, including nausea, constipation, somnolence, sedation, and most significantly, respiratory depression (14-16).

Respiration is controlled primarily by medullary respiratory centers along with input from chemoreceptors and other sources. Opioid-induced respiratory depression can be caused by effects of opioids at multiple sites, including respiratory neurons located in the medulla, which can lead to suppression of respiratory rate and inhibition of respiratory drive, effects on peripheral chemoreceptors located in the carotid and aortic bodies and lungs, which can cause suppression of ventilatory responses to hypoxemia and hypercapnia, and suppression of brain arousal systems/wakefulness, which can cause sedation. The three main classes of opioid receptors are mu, kappa, and delta (17, 18). Opioids exert their effect by stimulating predominantly the mu-opioid receptor, but also have weak activity at the kappa- and delta-opioid receptors. Activation of mu-opioid receptors in the brainstem can cause respiratory depression. The blood-brain barrier protects the central nervous system from various pathogens and chemicals. However, some drugs such as heroin (3,6-diacylmorphine) are fairly lipid-soluble, and hence, more readily cross the blood-brain barrier. Heroin crosses the blood-brain barrier more readily than its main metabolite, morphine. The high lipid solubility of fentanyl also allows it to cross the blood-brain barrier quickly and thus has a rapid onset

of action. Opioids also have an effect on cerebral cortical centers that regulate breathing (19).

Opioid activity in the central respiratory center in the medulla causes decreased tidal volume at lower concentration and decreased respiratory rate and tidal volume at higher concentration, resulting in decreased minute ventilation (16, 20). Opioid-induced respiratory depression is characterized by hypoventilation with slow, irregular breathing that leads to hypercarbia, then hypoxia, and may progress to shallow breathing, apnea, and if resuscitative efforts are not initiated in a timely fashion, ensuing cardiac arrest and death (21-27). Initially, tidal volume falls, but ventilation and oxygenation are maintained via tachypnea. As arousal progressively deteriorates, the respiratory rate falls, the tidal volumes fall, and in order, hypercarbia, acidosis, and hypoxemia develop, with possible progression to respiratory arrest. Acute opioid toxicity by fentanyl or its analogs may also cause the rapid onset of rigidity of muscles in the jaw, neck, chest wall, and abdomen, impairing an individual’s ability to breathe, and making it difficult for other individuals to provide ventilation for them (23, 28-37). The risk of such rigidity appears to increase along with the dose of fentanyl and the rapidity with which it is administered, however, the dose required to cause such rigidity need not be excessively high (34). Another possible risk is acute vocal cord closure, which has been reported to occur with the administration of sufentanil (38).

The acute effects and potential lethality of opioids can be reversed by the timely administration of naloxone, which is a nonselective competitive opioid antagonist at the opioid receptors that inhibits all pharmacologic effects of opioids (39, 40). Naloxone may be quickly, safely, and effectively administered intranasal by first responders, with low overall risk (41, 42). However, in order for it to be effective, one must first have the clinical suspicion that an opioid overdose may have occurred and also have naloxone readily available for administration in a timely fashion (43). However, many opioid-related deaths occur in isolation, possibly in attempts of the user to maintain a covert nature to their drug use, limiting the opportunity for other individuals to administer naloxone in a timely fashion.

Opioids that have a longer plasma half-life than naloxone have the potential to “renarcotize” an individual with the passage of time post-administration, as the effects of naloxone may wear off more rapidly than the effects of the opioid. Regarding the addictive potential of opioids, activation of the mu-opioid receptor is believed to initiate a series of intracellular signaling events that cause the release of dopamine from the nucleus accumbens, an area of the brain that is involved in reward circuitry, and links the event to the euphoria or “high” feeling caused by the drug use (44).

DISCUSSION

Conditions That Make an Individual More Susceptible to Opioid Toxicity

An individual’s baseline respiratory function may be compromised by various medical conditions such as heart disease (e.g., pulmonary edema from congestive heart failure), lung disease (e.g., chronic obstructive lung disease), obstructive sleep apnea, obesity, and advanced age. Conditions such as these would limit one’s physiologic reserve, and hence, one’s ability to overcome any compromising conditions that stress the body, such as the effects of drug toxicity. The nature of opioid-related deaths is varied, but generally involves the consumption of an excessive amount of opioid drug with or without other drugs/substances that result in severe respiratory depression, overwhelming the body’s ability to compensate for the drug effect. Potentiating conditions may include the relaxant effects of sleep and positional asphyxia or suffocation, as may be indicated at scene investigation.

The Physiologic Effects of Sleep and Sedation

Opioid deaths generally occur during sleep – a time when an individual no longer has conscious awareness, and is dependent upon autonomic mechanisms to maintain proper respiratory effort. During wakeful periods, an individual is generally alert and aware of their need to breathe, as cerebral activity associated with wakefulness helps regulate breathing (45, 46). However, during sleep, there is no longer an active, conscious stimulus to breathe, and an individual is

more vulnerable to a compromise in respiratory function, such as that caused by drug toxicity. During even light sleep, the body is dependent upon chemoreceptor activity to maintain adequate respiratory rhythm (46). Conditions that compromise ventilation may occur during sleep, such as drug-altered chemoreception. Also, during sleep, the upper airway (in particular, the oropharynx) tends to stenose to some degree, due to decreased tone from relaxation of upper airway dilator muscles, the genioglossus muscle, and other soft tissues, and from other factors, the effects of which appear to increase with age, making an individual more susceptible to drug-induced upper airway collapse/obstruction (47-51). Opioids, ethanol, and other potentiating drugs likely exacerbate respiratory events such as episodes of hypopnea and oxygen desaturation that normally occur during sleep. All of these drug effects can be compounded by obesity, the effects of advanced age, sleep-disordered breathing problems, and by an individual’s physiologic cardiac, respiratory, hepatic, and other comorbid limitations imposed by various natural disease processes (52).

Pain stimulates wakefulness and respiration, and can attenuate the respiratory depressant effects of opioids (53-55). Opioids are often administered therapeutically to help alleviate the acute effects of pain. Discomfort from pain generally aids in keeping an individual awake and aware. After opioids are consumed, often with the intent of minimizing pain to allow for restful sleep, an individual is more likely to be able to fall asleep and hence, lose the pain-induced stimulation of breathing (56). Patients are at highest risk of respiratory depression during the first 24 hours of opioid therapy (57), particularly if the individual has preexisting obstructive sleep apnea, heart failure, lung disease, obesity, or achieves a deep level of sedation. Sedation precedes opioid-induced respiratory depression. In monitored situations, assessment of respiratory status during opioid therapy involves visualization of the rise and fall of the patient’s chest to best assess the rate, depth, and regularity of respirations (57). Snoring should be given considerable attention, as it may indicate impending upper airway obstruction in a sedate patient, and may be alleviated by repositioning the patient to a lateral position, which helps maintain the patency of

the collapsible oropharyngeal tissues (58-60). Patients who usually snore are typically awakened by their own snoring and inadequate respirations; however, obtundation caused by the sedative effects of opioid therapy, additional sedative effects of other medications, and perhaps fatigue/sleep may prevent the patient's usual "self-arousal" during snoring, allowing progression of respiratory insufficiency to apnea.

In gauging the effectiveness of ventilation in monitored situations, continuous capnography (end-tidal carbon dioxide monitoring) is better than periodic pulse oximetry monitoring, which measures oxygen saturation (24, 61-63). Periodic assessment of oxygen saturation typically is performed at the time that patients are aroused to assess their vital signs, and arousing the patient will usually cause them to breathe deeper, providing a higher oxygen saturation at that particular time and a false sense of security regard-

ing their respiratory status. Because arousal stimulates respiration, respiratory status is best evaluated in the sleeping or calm, resting patient (57). Supplemental oxygen many also result in deceiving effects, as it may bolster the oxygen saturation of a patient who is, in fact, in respiratory failure, as would be demonstrated on capnography by an increased carbon dioxide level. Low oxygen saturation (hypoxemia) is considered a later indicator of inadequate ventilation than increased carbon dioxide concentration (hypercarbia) (24, 62, 64). Thus, in patients who are receiving supplemental oxygen, pulse oximetry may show high or at least adequate oxygen saturation despite current or impending respiratory depression (57, 62).

The Physical and Physiologic Effects of Obesity

Many physical effects of obesity can work individually or in combination to impair ventilation (**Figure 1**)

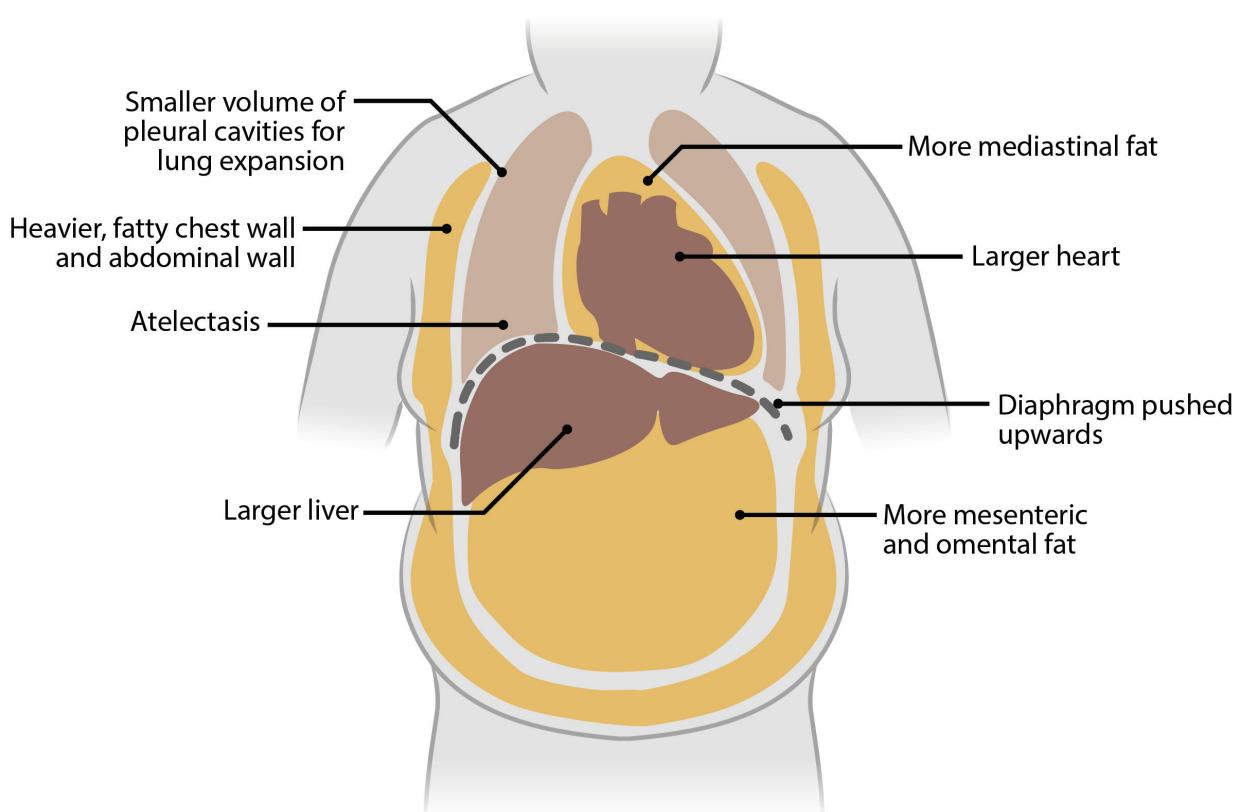


Figure 1: Physiological effects of obesity that can impair ventilation. Created under contract by professional medical illustrator Diana Kryski.

1). One of the effects is reduced chest wall compliance due to an increased amount of adipose tissue that adds weight on to the rib cage, which can make expansion of the rib cage with inhalation more difficult. Another factor is an increase in abdominal mass caused by increased liver size and a large amount of mesenteric and omental adipose tissue that can displace the diaphragm cephalad, decreasing the volume of the pleural cavities at baseline and hindering diaphragmatic excursion with inhalation. This can lead to atelectasis at the lung bases with ensuing ventilation/perfusion mismatch, hypoxemia, and overall impaired lung function. These effects are most significant when the body is in the prone or supine position, and are somewhat attenuated when the body is in the lateral ("recovery") position. Increased heart size is often associated with obesity, and, along with an increased amount of mediastinal adipose tissue, also limit the amount of space available for the lungs to expand.

Obese individuals are more prone to upper airway obstruction (**Figure 2**). The retropalatal oropharynx is generally recognized as the narrowest segment of the upper airway in most people (65-67). An increase in the thickness of the muscle mass of the lateral or posterior pharyngeal walls or an increase in the amount of adipose tissue and/or muscle mass in the soft palate and tongue that often accompanies obesity can result in chronic stenosis of the airway. This can predispose to further stenosis or even collapse and obstruction of the collapsible upper airway secondary to the negative pressure generated in the airway with inspiratory effort, resulting in hypoventilation and possibly apnea (65, 68). Because the upper airway lacks rigidity and structural support, soft tissues such as the tongue and soft palate can shift posteriorly according to the effects of gravity, predisposing to oropharyngeal collapse, particularly when an individual is in the supine position (69, 70). Opioids and other drugs can cause relaxation of the pharyngeal muscles, which can potentiate upper airway obstruction (71, 72). Such conditions would also likely potentiate airway obstruction in individuals with obstructive sleep apnea (73, 74).

The effects of obesity often compromise an individual's baseline respiratory status, making the obese

individual more vulnerable to the respiratory depressant effects of opioid toxicity. Some of the deleterious long-term respiratory effects of obesity include chronic hypoxia, obstructive sleep apnea, an ataxic breathing pattern, and central sleep apnea (75). Obese individuals often have a more rapid, shallow ventilatory pattern, and have decreased ventilatory reserve. Obese individuals (particularly those with prominent upper body fat distribution) have impairment among multiple pulmonary function test parameters and are more prone to develop atelectasis (76-84). These impairments in ventilatory function have been shown to improve upon weight loss (82, 83).

Cointoxicants

Any substance that can increase somnolence/sedation or cause respiratory insufficiency has the potential to augment and/or prolong the deleterious respiratory effects of opioids. Such substances include ethanol, benzodiazepines, benzodiazepine-like hypnotics, barbiturates, and various types of relaxants that can cause sedation and depress the body's hypoxicemic and hypercapnic ventilatory drives (16, 52, 85-101). Although these substances may have little respiratory depressant effect on their own, particularly when not consumed in excessive amounts, the use of these substances in combination with opioids has the potential to augment and/or prolong the deleterious respiratory depressant effects of opioids, and to also augment a stuporous or comatose condition. In many opioid-related deaths in which such cointoxicants are detected, oftentimes the opioid concentrations are lower than if the opioid was consumed in isolation (99). This finding is indicative of the cumulative respiratory depressant effects that multiple drugs can have on the body.

In excessive amounts, ethanol has the ability to increase the resistance of airflow through the upper airway, and may cause collapse of the tissues of the upper airway, resulting in disordered breathing and even obstructive apnea during sleep in unsuspected individuals (102, 103). Ethanol is a solvent and may also increase the rate of absorption of drugs when ingested around the same time as the drugs, leading to a more heightened drug effect. Ethanol has also been

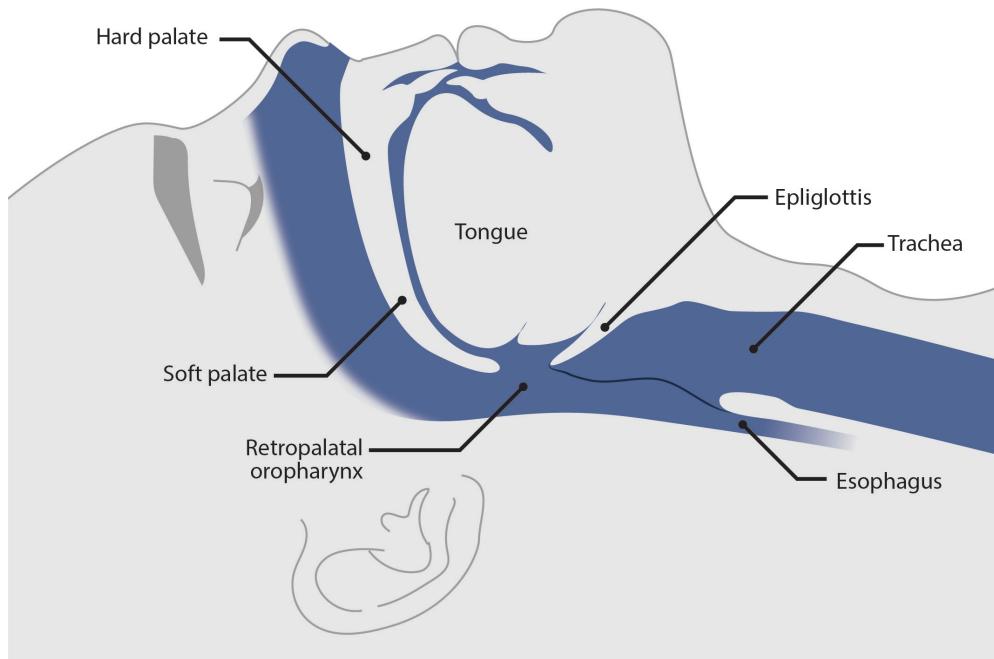
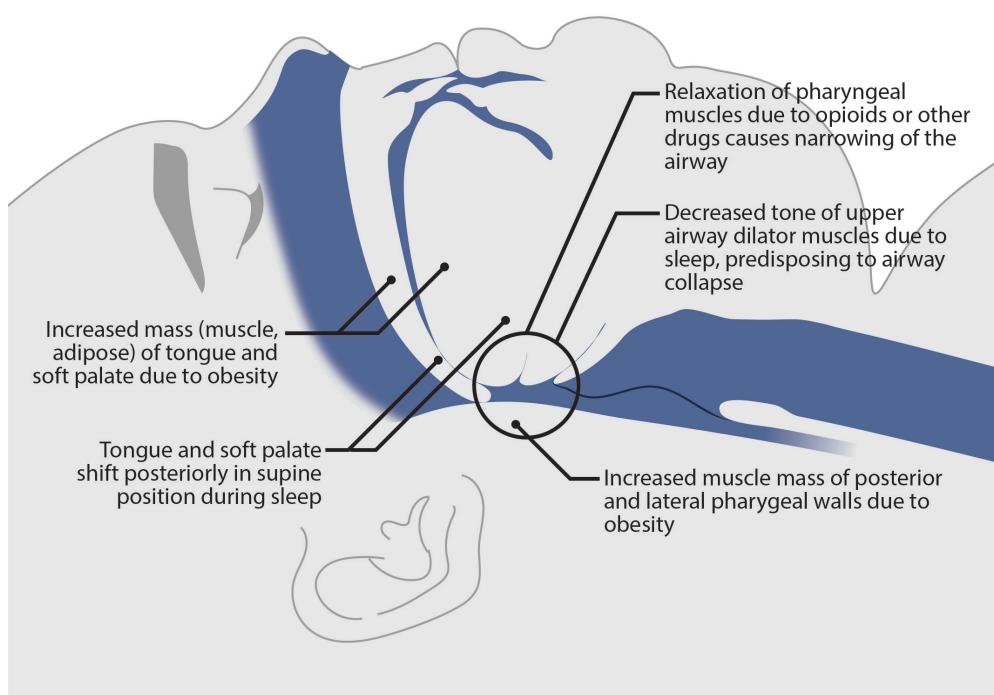
A

B


Figure 2: A) Normal oropharyngeal anatomy. B) Effects of obesity and opioids on oropharyngeal anatomy. Created under contract by professional medical illustrator Diana Kryski.

shown to decrease the ventilatory response to hypercapnia when combined with an opioid (104). Benzodiazepines can cause upper airway obstruction via relaxation of the muscles of the tongue and neck, which increases the work of breathing (72, 105, 106). Sleep medications and any medications that can cause sedation and drowsiness such as carisoprodol, diphenhydramine, and some antidepressants can potentiate the sedative effects of opioids. When detected, such cointoxicants and their associated pharmacodynamic effects should be considered as additional significant factors in opioid-related deaths. As many cases of opioid-related death exhibit polypharmacy, toxicology testing should be comprehensive enough to include such drugs, and also various stimulants and other drugs that may have a deleterious effect on an individual's health (98).

The History and Scene Investigation

The identification of drugs or drug paraphernalia at the scene, needle punctures or needle track marks on the decedent, and/or pertinent medical/social information gleaned from interviews from friends, family, or acquaintances often suggest that a death may be drug-related. The presence of a syringe, needle, drugs, drug packaging material, tourniquets, or other drug paraphernalia at the death scene is important information that initiates investigating the death as possibly being drug-related. However, one should not rely on the presence of these typical findings, as many times they are absent, as the drug(s) may have been consumed previously at another location, the scene may have been altered or cleaned up by another individual prior to summoning help, or the drugs may have been in pill form, and no drug-related paraphernalia required for consumption of the drug. A significant number of opioid-related deaths will likely be missed if one performs toxicology testing only if illicit drugs or drug paraphernalia are documented at the scene (12, 100, 107).

Recent forced abstinence from drugs such as incarceration in prison or enrollment in a drug treatment program can lead to a desire for drug use upon release from the facility with fatal results, which tend to occur with-

in two weeks after release, but the risk persists even longer (12, 108, 109). In such instances, the individual may have lost a degree of tolerance to opioids and other drugs, may exhibit bad judgment, or may return to a familiar environment of drug use and as a result, be more susceptible to overdose (110). In addition, an individual's tolerance to the respiratory depressant effects of opioids may lag their tolerance to the euphoric effects of opioids, putting the chronic drug abuser more at risk of a fatal overdose when attempting to achieve a previously experienced desired state of euphoria (16). An individual's drug tolerance is difficult to gauge even if their drug prescription history is known. Clues that may suggest an opioid death include a history of preterminal snoring, which can be indicative of upper airway obstruction caused by opioids, benzodiazepines, other drugs, or a combination thereof (111). Query should include whether the decedent was known to normally snore, and if so, whether or not their preterminal snoring was any different than usual.

All of the decedent's prescription pills and any free/unlabeled pills should be collected to be inventoried and possibly analyzed. The chemical composition of pills may not always match what may be indicated by the appearance of the pill. An individual may abuse their prescribed opioids, or he/she may obtain opioid medications from another source ("diverted medications") for nonmedical use (112, 113). The use of diverted medications has increased risk. The drug user does not know for certain what drugs they are purchasing and using, as nonregulated pills may be intentionally mislabeled as a different drug, drug powders will likely be of varying concentration and intensity, and may in fact consist wholly or in part of unintended substances that may be used to dilute a drug or to augment the effects of a drug (114).

The chemical composition of powdered drug encountered at a scene or on a decedent can vary and may represent a mixture of different drugs of varying concentration. A powder's composition cannot be predicted by visualization alone. Heroin is a potent opioid that can cause death quickly or in a more prolonged manner following a comatose period. More powerful drugs such as fentanyl, acetyl fentanyl, carfentanil, or

other fentanyl analogs may be consumed individually or may be added to powdered heroin or other drugs to augment the drug's euphoric effects, but would also increase the drug's respiratory depressant effects, which would increase the drug's lethality (98, 111, 115-122). If drugs, particularly powdered forms of drugs are encountered, either at a death scene or on the decedent, they must be handled with caution, using appropriate personal protective equipment because some drugs such as carfentanil are very potent and can be toxic or even fatal if inhaled or absorbed in sufficient amount either transcutaneously or through mucus membranes. For this reason, it is also advantageous for investigators of such cases to have naloxone readily available if needed. Powders or syringes recovered from the death scene can be chemically analyzed to determine the purity of the drug or if the powder is a mixture of drugs, which drugs are present. Care must be taken when examining the decedent, their clothing, and other items at the scene to avoid needle stick injuries, which have the potential to transmit infectious disease such as hepatitis viruses and human immunodeficiency virus.

On occasion, a syringe will be present in the decedent's hand or remain embedded in his/her arm or other injection site. Intravenous injection of a drug may deliver a particularly large amount of drug in a short amount of time that may overwhelm the body's compensatory abilities. Intravenous drug use and poly-drug abuse each predispose to increased lethality (12). Injected opioids are more likely to cause significant respiratory depression than oral opioids (24). This is because the ingestion of opioids results in a more gradual increase in opioid concentration in the blood and the resultant progressive respiratory depression will cause hypercarbia and hypoxemia more slowly, which will, if not overwhelming, elicit an increased reactive respiratory response via chemoreceptor activity (21). In contrast, an intravenous bolus of an opioid or the injection of a particularly potent opioid may lead to a rapid and overwhelming increase in central opioid receptor occupancy, causing a rapid development of apnea that may be refractory to the body's response to the ensuing hypercarbia and hypoxemia. Hence, opioids that cross the blood-brain barrier more slowly, and those that exhibit slower receptor binding, may be

less lethal than those that bind more quickly despite having equivalent analgesic effects because the slower acting drugs allow the body more time to mount a counteracting physiologic response. The body's response, however, may be limited anyway, as opioids variably depress the body's central and peripheral chemoreceptors, impairing the body's ability to respond to hypoxemia and hypercarbia (27, 91, 123).

Visualization of the decedent undisturbed at the scene of death is essential to adequately appreciate and document various physical conditions that can potentially compromise an individual's ability to adequately ventilate. Conditions suggestive of positional asphyxia and suffocating/smothering include the decedent positioned prone with their face pressed into a soft object such as a pillow, cushion, or mattress, or the body positioned with their head/neck at an awkward angle, potentially compromising airflow through the upper airway. In obese individuals, the supine position can predispose to upper airway obstruction. Compared to the neutral position, head flexion increases the likelihood of upper airway collapse, while head extension decreases the likelihood of upper airway collapse (124). Once the decedent is moved at the scene, these factors may go unnoticed by subsequent observers, aside from the distribution of lividity, which may shift with time. Blanched lividity about the nose, mouth, and central face in individuals who are found prone would add support to a theory of smothering or suffocation. In opioid fatalities, there is often a variable amount of foamy fluid about the mouth and/or nose ("foam cone"), resulting from the marked pulmonary edema that often develops in such cases (125). The edema fluid extends from the lungs through the bronchi, trachea, larynx, and oropharynx, eventually exiting the nose and/or mouth. It is, however, not specific for overdose, as pulmonary edema and the associated foamy fluid on the face may also be seen with other causes of death such as drowning, congestive heart failure, epileptic seizure, and traumatic head injury.

The Autopsy Findings

It is best to perform a complete autopsy when a death is suspected to be drug-related to rule out any more

convincing cause of death, to allow for optimal collection of toxicology specimens, and to allow for optimal interpretation of toxicology results (100, 107). Individual case circumstances and office protocol may dictate making the diagnosis of acute drug toxicity without an autopsy having been performed in cases in which the decedent had experienced a delayed death with preterminal hospitalization, in cases in which the decedent's family has an objection to autopsy, or other reasons. Needle track marks, recent needle punctures, and skin popping scars from remote subcutaneous drug injections may indicate drug use, although they are not necessary, as heroin and other opioids may be smoked, insufflated, ingested, or consumed by other means. Although these cutaneous findings are often located on the upper extremities, they may be located on more discrete areas of the body such as the lower legs or feet, possibly in an attempt by the user to hide the visual stigmata of intravenous drug use, because of difficult venous access in the upper extremities, or as a matter of convenience or personal preference.

In the vast majority of respiratory-related fatal opioid overdoses, the most significant internal finding revealed at autopsy is pulmonary edema, which is characterized by heavy, congested, edematous, boggy lungs (114, 126). Lung weights in such cases often exceed 500 g each, and may on occasion exceed 1000 g each (126). The observation of such marked pulmonary edema from opioid overdose was first reported by William Osler in 1880 (127), and since then, it has been widely reported in the literature (125, 128-132). Although the phenomenon of pulmonary edema in these cases is well-described, it is poorly understood. The mechanism is probably multifactorial, and most likely involves an imbalance between hydrostatic forces in the pulmonary blood vessels and increased pulmonary capillary permeability. Hypoxemia is likely a factor, as it is known to cause an inhomogeneous constriction of pulmonary arteries in order to attenuate ventilation/perfusion mismatches in the lungs, which leads to an increase in pulmonary artery pressure throughout the lungs (133, 134). Pulmonary arteries that are not constricted by the effects of hypoxemia become relatively overperfused as compared to the other, constricted arteries, and are hence subject-

ed to high-pressure flow. The pulmonary response to hypoxemia differs among people, and the magnitude of the resultant pulmonary vasoconstriction can vary greatly among individuals (135, 136).

Hypoxia may also cause decreased myocardial contractility which, along with pulmonary vasoconstriction, exposes pulmonary capillaries to high pressures that can damage their walls, leading to a high-permeability form of pulmonary edema. Increased pressure on the capillary wall imparts excessive strain on the collagen and the extracellular matrix of the alveolar capillary barrier, which could lead to mechanically induced breaks in the blood-gas barrier, resulting in increased pulmonary capillary permeability (137). In experiments, morphine has been implicated in increased vascular permeability and endothelial dysfunction, with greater effects more likely at higher concentrations (138, 139). However, in one study, no increase in defects of alveolar capillary membranes was detected by immunohistochemical microscopic study with antibodies directed against collagen IV and laminin in acute heroin toxicity deaths compared to sudden cardiac death controls (140). Because the protein content of pulmonary edema fluid in opioid overdose cases has been reported as being significantly higher than that of cardiac-related pulmonary edema (141), the pathogenesis of the edema likely involves, at least to some extent, increased pulmonary capillary permeability. The edema may be augmented by hydrostatic forces mentioned previously, possibly in combination with those generated by efforts made to respire despite a partially obstructed glottis/upper airway (negative pressure pulmonary edema) (142). Negative pressure pulmonary edema refers to instances in which high negative intrathoracic pressure is generated in order to overcome upper airway obstruction, causing an increase in transmural pulmonary capillary pressure and the rapid transudation of fluid from the pulmonary capillaries into the interstitium and alveolar spaces (142, 143).

Opioids may cause a hypersensitivity reaction, as has been demonstrated by the detection of elevated tryptase concentrations in heroin fatalities (144, 145). In many people, morphine injection causes the activation

of mast cells and the subsequent release of histamine and tryptase (146-152). Histamine can cause hypersensitivity reactions that include peripheral vasodilation that can lead to systemic hypotension and shock (151). Histamine can also cause bronchospasm and an increase in the permeability of capillaries, as has been demonstrated in animal experiments (153-157). Many opioids are potent histamine releasers and are capable of causing a vast array of hemodynamic/anaphylactoid reactions (151, 152). In cases in which it appears that the pulmonary edema and death are evident soon after the opioid use (such as the presence of an inserted needle), its pathogenesis may be due to a hypersensitivity reaction.

In all, respiratory depression that occurs in opioid toxicity causes hypoxemia, which can cause pulmonary vasoconstriction and decreased myocardial contractility, which can cause increased pulmonary capillary pressure that can augment the transudation of fluid through the capillary walls, particularly if their permeability is increased from the effects of hydrostatic forces, hypoxia, hypersensitivity reaction, primary drug toxicity, or other factors. The transudation of fluid leads to pulmonary edema, which in turn exacerbates the hypoxemia, forming a vicious cycle that is not broken until adequate oxygenation can be restored. Systemic shock from hypersensitivity to opioid or a different substance that was used to dilute or enhance the drug may help explain rapid deaths.

Other findings often observed at autopsy in cases of opioid overdose include frothy tan, sometimes bloody fluid in the airways and about the nose and/or mouth (a “foam cone”), and sometimes mucus in the airways or about the nostrils and face. The mucus may arise from several factors, including stimulation of the parasympathetic nervous system in an attempt by the body to protect the tracheal and bronchial mucosa from the irritant and caustic effects of aspirated material. Histologically, one may also see early acute inflammation in the lungs (e.g., pneumonia, bronchitis), as a reaction to aspirated material if the comatose period is of sufficient duration (126). Some opioids such as codeine decrease the tone of the lower esophageal sphincter and suppress the cough reflex, predis-

posing to aspiration. One may also encounter a large amount of urine in the urinary bladder, or saturation of the decedent’s clothing with urine, particularly if the comatose state was unusually prolonged, or if a large volume of liquid such as ethanol was also ingested. Toxicology specimens collected should at a minimum include blood (femoral vein blood preferred), urine, and vitreous fluid as they are available, and additional specimens as needed (100). Toxicology specimens should be appropriately preserved and stored.

The Toxicology Report

Interpretation of the data generated on the toxicology report must proceed with careful and critical evaluation with consideration of other information, such as the body’s physiologic response to drug toxicity, the possibility of drug metabolism down to lower concentrations, and the effect that postmortem processes can have on drug concentrations. One need not expect a drug-related death to have drug concentrations that have achieved fatal levels as have been reported in various publications. During the dying process, which may be prolonged, drugs may be metabolized down to lower concentrations, and parent/metabolite drug ratios altered. The drug concentrations measured from postmortem samples do not necessarily reflect the concentrations that the individual had at the time that he/she died, or at the time that he/she had reached peak intoxication. Many drug analogs will not be detected by “routine” toxicology testing, and must be specifically tested for. Suspicion for such analogs should be heightened in a case in which the circumstances are suspicious for an opioid-related death, yet toxicology tests are negative or reveal only trace/low concentrations of a drug(s) that is/are deemed to be insufficient to have caused the death. In such instances, additional, more focused testing is warranted.

In a toxicology report, heroin use is inferred by the documentation of morphine and 6-acetylmorphine in the decedent’s body fluids, as heroin itself is usually not detected. This is because heroin (3,6-diacetylmorphine) is rapidly deacetylated by blood esterases to the intermediate 6-acetylmorphine, which is then fairly rapidly broken down to morphine, which has a longer



half-life. Because heroin is broken down very quickly, it is usually no longer detectable. While the detection of morphine may represent the use of either morphine or heroin, 6-acetylmorphine is widely regarded as being a specific marker for heroin. Another clue that the morphine detected was likely derived from heroin is the detection of a very low concentration of codeine in comparison to the decedent's morphine concentration. Codeine is naturally present in the opium poppy from which heroin is synthesized, is not purified during the preparation of heroin, and therefore is often present in low concentrations when heroin is consumed. A femoral blood morphine:codeine ratio of greater than one is typical when heroin is consumed (158-160). The ratio is often much greater than one in most cases, as the codeine is often present in only trace concentrations. If, however, the codeine concentration is great, or at least larger than the decedent's morphine concentration, one should consider that the decedent had consumed codeine, with some of the codeine metabolized to morphine, or that the decedent had consumed a combination of codeine and heroin. In cases of heroin use, the morphine:codeine ratio is also greater than one in the urine (158, 161).

An additional factor that one must consider is the presence of cointoxicants, which may have cumulative effects on one's ability to adequately ventilate (93), or otherwise stress the body. In these situations, the presence of two, three, or more substances with similar deleterious physiologic side effects can prove just as fatal in so-called "average" or "below average" concentrations as a single drug at a "high" concentration, due to the cumulative effects of the drugs (96). Because of the effects of ongoing drug metabolism, in circumstances in which an individual has died during hospitalization following drug overdose, it is imperative to obtain blood, serum, and urine specimens that were collected during hospitalization in order to help obtain the best toxicology specimens and test results possible. The earlier the specimens were collected, the better their yield. One should also be careful to review the medical records to identify any therapeutically-administered drugs that may show up on the toxicology report.

In interpreting drug concentrations, and their likelihood of causing the death of an individual, one must interpret the values in the context of all available relevant information, including the autopsy findings, the decedent's medical history and social history, including possible drug tolerance, the scene findings, the location in the body from which the blood was obtained, the potential effects of drug metabolism, drug distribution and redistribution, the effects of drug metabolites, and the cumulative toxic effects of multiple drugs (100, 101, 162-166). One may also consider variability in an individual's response to drugs that may include many factors, including their genetic make-up (pharmacogenomics) and the extent of baseline natural disease that they may have. In the right situation, sometimes the mere presence of a powerful drug, at the exclusion of any more significant cause of death, can be enough to be the cause of death. In other situations, the cumulative toxic effect of more than one drug may have caused an individual's demise. In such cases, listing all of the contributing drugs on the death certificate would be appropriate. Every case is unique, and the autopsy and toxicology findings must be interpreted within the context of each particular case. Also, consider that in some cases, a drug may not be the cause of death, even though it is within what is reported to be a lethal concentration.

CONCLUSION

Opioids are becoming increasingly more common in drug-related fatalities. Suspicion that a death is drug-related begins with the decedent's history and scene investigation. At autopsy, the main findings are observed in the lungs, which often have marked edema and congestion. Frothy watery fluid is often in the airways. Various natural disease processes may limit one's physiological reserve, rendering them more susceptible to an overdose. Although many opioids will be detected on routine toxicological testing, more specialized testing may be warranted for opioid analogs, or other uncommon, synthetic, or semisynthetic drugs.

REFERENCES

- 1) Compton WM, Jones CM, Baldwin GT. Relationship between nonmedical prescription-opioid use and heroin use. *N Engl J Med.* 2016 Jan 14; 374(2):154-63. PMID: 26760086.
<https://dx.doi.org/10.1056/NEJMra1508490>.
- 2) Rudd RA, Paulozzi LJ, Bauer MJ, et al. Increases in heroin overdose deaths - 28 States, 2010 to 2012. *MMWR Morb Mortal Wkly Rep.* 2014 Oct 3; 63(39):849-54. PMID: 25275328.
- 3) Haegerich TM, Paulozzi LJ, Manns BJ, Jones CM. What we know, and don't know, about the impact of state policy and systems-level interventions on prescription drug overdose. *Drug Alcohol Depend.* 2014 Dec 1; 145:34-47. PMID: 25454406.
<https://dx.doi.org/10.1016/j.drugalcdep.2014.10.001>.
- 4) Paulozzi LJ. Prescription drug overdoses: a review. *J Safety Res.* 2012 Sep; 43(4):283-9. PMID: 23127678.
<https://dx.doi.org/10.1016/j.jsr.2012.08.009>.
- 5) Chen LH, Hedegaard H, Warner M. Drug-poisoning deaths involving opioid analgesics: United States, 1999-2011. *NCHS Data Brief.* 2014 Sep; (166):1-8. PMID: 25228059.
- 6) Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. *JAMA Psychiatry.* 2014 Jul 1; 71(7):821-6. PMID: 24871348.
<https://dx.doi.org/10.1001/jamapsychiatry.2014.366>.
- 7) Harris BR. Talking about screening, brief intervention, and referral to treatment for adolescents: an upstream intervention to address the heroin and prescription opioid epidemic. *Prev Med.* 2016 Oct; 91: 397-399. PMID: 27544318.
<https://dx.doi.org/10.1016/j.ypmed.2016.08.022>.
- 8) Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health.* 2015 Mar 18; 36:559-74. PMID: 25581144.
<https://dx.doi.org/10.1146/annurev-publhealth-031914-122957>.
- 9) Martins SS, Sampson L, Cerdá M, Galea S. Worldwide prevalence and trends in unintentional drug overdose: a systematic review of the literature. *Am J Public Health.* 2015 Nov; 105(11):2373. PMID: 26451757. PMCID: PMC4605171.
<https://dx.doi.org/10.2105/AJPH.2015.302843a>.
- 10) Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician.* 2008 Mar; 11(2 Suppl):S63-88. PMID: 18443641.
- 11) Hedegaard H, Chen LH, Warner M. Drug-poisoning deaths involving heroin: United States, 2000-2013. *NCHS Data Brief.* 2015 Mar; (190):1-8. PMID: 25932890.
- 12) Gilson T, Herby C, Naso-Kaspar C. The Cuyahoga County hero in epidemic. *Acad Forensic Pathol.* 2014 Mar; 4(1):109-13.
<https://doi.org/10.23907/2013.018>.
- 13) Alexander RT, Hedrick CW, Alexander SD, et al. Epidemic fentanyl deaths in Maryland: a public health intervention involving geographic information systems and collaboration with the Drug Enforcement Administration. *Acad Forensic Pathol.* 2016 Jun; 6(2):301-14.
<https://doi.org/10.23907/2016.031>.
- 14) Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology.* 2010 Jan; 112(1):226-38. PMID: 20010421.
<https://dx.doi.org/10.1097/ALN.0b013e3181c38c25>.
- 15) Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician.* 2008 Mar; 11(2 Suppl):S105-20. PMID: 18443635.
- 16) White JM, Irvine RJ. Mechanisms of fatal opioid overdose. *Addiction.* 1999 Jul; 94(7):961-72. PMID: 10707430.
<https://doi.org/10.1046/j.1360-0443.1999.9479612.x>.
- 17) Waldhoer M, Bartlett SE, Whistler JL. Opioid receptors. *Annu Rev Biochem.* 2004; 73:953-90. PMID: 15189164.
<https://dx.doi.org/10.1146/annurev.biochem.73.011303.073940>.
- 18) Brownstein MJ. A brief history of opiates, opioid peptides, and opioid receptors. *Proc Natl Acad Sci U S A.* 1993 Jun 15; 90(12): 5391-3. PMID: 8390660. PMCID: PMC46725.
<https://doi.org/10.1073/pnas.90.12.5391>.
- 19) Pattinson KT, Governo RJ, MacIntosh BJ, et al. Opioids depress cortical centers responsible for the volitional control of respiration. *J Neurosci.* 2009 Jun 24; 29(25):8177-86. PMID: 19553457.
<https://dx.doi.org/10.1523/JNEUROSCI.1375-09.2009>.
- 20) Santiago TV, Edelman NH. Opioids and breathing. *J Appl Physiol (1985).* 1985 Dec; 59(6):1675-85. PMID: 2934364.
- 21) Leino K, Mildh L, Lertola K, et al. Time course of changes in breathing pattern in morphine- and oxycodone-induced respiratory depression. *Anesthesia.* 1999 Sep; 54(9):835-40. PMID: 10460553.
<https://doi.org/10.1046/j.1365-2044.1999.00946.x>.
- 22) Bouillon T, Bruhn J, Roepcke H, Hoeft A. Opioid-induced respiratory depression is associated with increased tidal volume variability. *Eur J Anaesthesiol.* 2003 Feb; 20(2):127-33. PMID: 12622497.
<https://doi.org/10.1097/00003643-200302000-00009>.
- 23) Streisand JB, Bailey PL, LeMaire L, et al. Fentanyl-induced rigidity and unconsciousness in human volunteers. Incidence, duration, and plasma concentrations. *Anesthesiology.* 1993 Apr; 78(4):629-34. PMID: 8466061.
<https://doi.org/10.1097/00000542-199304000-00003>.
- 24) Jolley CJ, Bell J, Rafferty GF, et al. Understanding heroin overdose: a study of the acute respiratory depressant effects of injected pharmaceutical heroin. *PLoS One.* 2015 Oct 23; 10(10):e0140995. PMID: 26495843. PMCID: PMC4619694.
<https://doi.org/10.1371/journal.pone.0140995>.
- 25) Conti G, Pierdominici S, Ferro G, et al. Effects of low-dose alfentanil administration on central respiratory drive and respiratory pattern in spontaneously breathing ASA 1 patients. *Anesthesia.* 2002 Jun; 57(6):540-3. PMID: 12010267.
<https://doi.org/10.1046/j.1365-2044.2002.02573.x>.
- 26) Stohler R, Dürsteler KM, Störmer R, et al. Rapid cortical hemoglobin deoxygenation after heroin and methadone injection in humans: a preliminary report. *Drug Alcohol Depend.* 1999 Nov 1; 57(1):23-8. PMID: 10617310. [https://doi.org/10.1016/s0376-8716\(99\)00036-8](https://doi.org/10.1016/s0376-8716(99)00036-8).
- 27) Weil JV, McCullough RE, Kline JS, Sodal IE. Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. *N Engl J Med.* 1975 May 22; 292(21):1103-6. PMID: 1128555.
<https://dx.doi.org/10.1056/NEJM197505222922106>.
- 28) Liu X, Zou Y, Zhao J, Huang Y. Emergency scenario of fentanyl induced faciocervical rigidity and complete upper airway obstruction during anesthesia induction. *Chin Med J (Engl).* 2014; 127(3):595-6. PMID: 24451975.
- 29) Bailey PL, Wilbrink J, Zwanikken P, et al. Anesthetic induction with fentanyl. *Anesth Analg.* 1985 Jan; 64(1):48-53. PMID: 2981489.
<https://doi.org/10.1213/00000539-198501000-00010>.
- 30) Neidhart P, Burgener MC, Schwieger I, Suter PM. Chest wall rigidity during fentanyl- and midazolam-fentanyl induction: ventilatory and haemodynamic effects. *Acta Anaesthesiol Scand.* 1989 Jan; 33(1):1-5. PMID: 2644747.
<https://doi.org/10.1111/j.1399-6576.1989.tb02849.x>.

- 31) Dimitriou V, Zogogiannis I, Liotiri D, et al. Impossible mask ventilation after an unusually low dose fentanyl-induced muscle rigidity in a patient with essential tremor: a case report and review of the literature. *Middle East J Anaesthesiol.* 2014 Oct; 22(6):619-22. PMID: 25669008.
- 32) Burns G, DeRienz RT, Baker DD, et al. Could chest wall rigidity be a factor in rapid death from illicit fentanyl abuse? *Clin Toxicol (Phila).* 2016 Jun; 54(5):420-3. PMID: 26999038. <https://dx.doi.org/10.3109/15563650.2016.1157722>.
- 33) Coruh B, Tonelli MR, Park DR. Fentanyl-induced chest wall rigidity. *Chest.* 2013 Apr; 143(4):1145-6. PMID: 23546488. <https://dx.doi.org/10.1378/chest.12-2131>.
- 34) Ackerman WE, Phero JC, Theodore GT. Ineffective ventilation during conscious sedation due to chest wall rigidity after intravenous midazolam and fentanyl. *Anesth Prog.* 1990 Jan-Feb; 37(1):46-8. PMID: 2077987. PMCID: PMC2163527.
- 35) Bonnet F, Kergrohen F, Lafosse JE, et al. Post-operative rigidity after fentanyl administration. *Eur J Anaesthesiol.* 1986 Sep; 3(5):413-6. PMID: 3780697.
- 36) Rosenberg M. Muscle rigidity with fentanyl: a case report. *Anesth Prog.* 1977 Mar-Apr; 24(2):50-2. PMID: 274086. PMCID: PMC2516049.
- 37) Vaughn RL, Bennett CR. Fentanyl chest wall rigidity syndrome--a case report. *Anesth Prog.* 1981 Mar-Apr; 28(2):50-1. PMID: 6943947. PMCID: PMC2516388.
- 38) Bennett JA, Abrams JT, Van Riper DF, Horrow JC. Difficult or impossible ventilation after sufentanil-induced anesthesia is caused primarily by vocal cord closure. *Anesthesiology.* 1997 Nov; 87(5):1070-4. PMID: 9366458. <https://doi.org/10.1097/00000542-199711000-00010>.
- 39) Martin WR. Naloxone. *Ann Intern Med.* 1976 Dec; 85(6):765-8. PMID: 187095.
- 40) Kaufman RD, Gabathuler ML, Bellville JW. Potency, duration of action and pA₂ in man of intravenous naloxone measured by reversal of morphine-depressed respiration. *J Pharmacol Exp Ther.* 1981 Oct; 219(1):156-62. PMID: 7288605.
- 41) Barton ED, Ramos J, Colwell C, et al. Intranasal administration of naloxone by paramedics. *Prehosp Emerg Care.* 2002 Jan-Mar; 6(1):54-8. PMID: 11789651.
- 42) Barton ED, Colwell CB, Wolfe T, et al. Efficacy of intranasal naloxone as a needless alternative for treatment of opioid overdose in the prehospital setting. *J Emerg Med.* 2005 Oct; 29(3):265-71. PMID: 16183444. <https://dx.doi.org/10.1016/j.jemermed.2005.03.007>.
- 43) Sumner SA, Mercado-Crespo MC, Spelke MB, et al. Use of naloxone by emergency medical services during opioid drug overdose resuscitation efforts. *Prehosp Emerg Care.* 2016; 20(2):220-5. PMID: 26383533. PMCID: PMC4798917. <https://dx.doi.org/10.3109/10903127.2015.1076096>.
- 44) Volkow ND, Wang GJ, Fowler JS, et al. Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D(2) receptors. *J Pharmacol Exp Ther.* 1999 Oct; 291(1):409-15. PMID: 10490931.
- 45) Fink BR. Influence of cerebral activity in wakefulness on regulation of breathing. *J Appl Physiol.* 1961 Jan; 16:15-20. PMID: 13699604.
- 46) Datta AK, Shea SA, Horner RL, Guz A. The influence of induced hypocapnia and sleep on the endogenous respiratory rhythm in humans. *J Physiol.* 1991; 440:17-33. PMID: 1804960. PMCID: PMC1180137. <https://doi.org/10.1113/jphysiol.1991.sp018693>.
- 47) Worsnop C, Kay A, Kim Y, et al. Effect of age on sleep onset-related changes in respiratory pump and upper airway muscle function. *J Appl Physiol (1985).* 2000 May; 88(5):1831-9. PMID: 10797148.
- 48) Ayappa I, Rapoport DM. The upper airway in sleep: physiology of the pharynx. *Sleep Med Rev.* 2003 Feb; 7(1):9-33. PMID: 12586528. <https://doi.org/10.1053/smrv.2002.0238>.
- 49) Trudo FJ, Gefter WB, Welch KC, et al. State-related changes in upper airway caliber and surrounding soft-tissue structures in normal subjects. *Am J Respir Crit Care Med.* 1998 Oct; 158(4):1259-70. PMID: 9769290. <https://dx.doi.org/10.1164/ajrccm.158.4.9712063>.
- 50) Remmers JE, deGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol Respir Environ Exerc Physiol.* 1978 Jun; 44(6):931-8. PMID: 670014.
- 51) Sauerland EK, Harper RM. The human tongue during sleep: electromyographic activity of the genioglossus muscle. *Exp Neurol.* 1976 Apr; 51(1):160-70. PMID: 177304. [https://doi.org/10.1016/0014-4886\(76\)90061-3](https://doi.org/10.1016/0014-4886(76)90061-3).
- 52) Warner-Smith M, Darke S, Lynskey M, Hall W. Heroin overdose: causes and consequences. *Addiction.* 2001 Aug; 96(8):1113-25. PMID: 11487418. <https://dx.doi.org/10.1080/09652140120060716>.
- 53) Borgbjerg FM, Nielsen K, Franks J. Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: a controlled study in human volunteers. *Pain.* 1996 Jan; 64(1):123-8. PMID: 8867254. [https://doi.org/10.1016/0304-3959\(95\)00088-7](https://doi.org/10.1016/0304-3959(95)00088-7).
- 54) Sarton E, Dahan A, Teppema L, et al. Influence of acute pain induced by activation of cutaneous nociceptors on ventilatory control. *Anesthesiology.* 1997 Aug; 87(2):289-96. PMID: 9286893. <https://doi.org/10.1097/00000542-199708000-00016>.
- 55) Bourke DL. Respiratory effects of regional anesthesia during acute pain. *Reg Anesth.* 1993 Nov-Dec; 18(6):361-5. PMID: 8117632.
- 56) Dahan A, Overdyk F, Smith T, et al. Pharmacovigilance: a review of opioid-induced respiratory depression in chronic pain patients. *Pain Physician.* 2013 Mar-Apr; 16(2):E85-94. PMID: 23511694.
- 57) Pasero C. Assessment of sedation during opioid administration for pain management. *J Perianesth Nurs.* 2009 Jun; 24(3):186-90. PMID: 19500754. <https://dx.doi.org/10.1016/j.jopan.2009.03.005>.
- 58) Isono S, Tanaka A, Nishino T. Lateral position decreases collapsibility of the passive pharynx in patients with obstructive sleep apnea. *Anesthesiology.* 2002 Oct; 97(4):780-5. PMID: 12357140. <https://doi.org/10.1097/00000542-200210000-00006>.
- 59) Gross JB, Bachenbergl KL, Benumof JL, et al. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: a report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. *Anesthesiology.* 2006 May; 104(5):1081-93; quiz 1117-8. PMID: 16645462. <https://doi.org/10.1097/00000542-200605000-00026>.
- 60) Ong JS, Touyz G, Tanner S, et al. Variability of human upper airway collapsibility during sleep and the influence of body posture and sleep stage. *J Sleep Res.* 2011 Dec; 20(4):533-7. PMID: 21554464. <https://dx.doi.org/10.1111/j.1365-2869.2011.00925.x>.
- 61) Horlocker TT, Burton AW, Connis RT, et al. Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration. *Anesthesiology.* 2009 Feb; 110(2):218-30. PMID: 19194148. <https://dx.doi.org/10.1097/ALN.0b013e31818ec946>.
- 62) Burton JH, Harrah JD, Germann CA, Dillon DC. Does end-tidal carbon dioxide monitoring detect respiratory events prior to current sedation monitoring practices? *Acad Emerg Med.* 2006 May; 13(5): 500-4. PMID: 16569750. <https://dx.doi.org/10.1197/j.aem.2005.12.017>.
- 63) Herman NL, Choi KC, Affleck PJ, et al. Analgesia, pruritus, and ventilation exhibit a dose-response relationship in parturients receiving intrathecal fentanyl during labor. *Anesth Analg.* 1999 Aug; 89(2):378-83. PMID: 10439751. <https://doi.org/10.1097/00000539-199908000-00024>.

- 64) Jarzyna D, Jungquist CR, Pasero C, et al. American Society for Pain Management Nursing guidelines on monitoring for opioid-induced sedation and respiratory depression. *Pain Manag Nurs.* 2011 Sep; 12(3): 118-145.e10. PMID: 21893302. <https://dx.doi.org/10.1016/j.pmn.2011.06.008>.
- 65) Schwab RJ, Gupta KB, Gefter WB, et al. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. *Am J Respir Crit Care Med.* 1995 Nov; 152(5 Pt 1):1673-89. PMID: 7582313. <https://dx.doi.org/10.1164/ajrccm.152.5.7582313>.
- 66) Schwab RJ, Gefter WB, Hoffman EA, et al. Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep disordered breathing. *Am Rev Respir Dis.* 1993 Nov; 148(5): 1385-400. PMID: 8239180. <https://dx.doi.org/10.1164/ajrccm/148.5.1385>.
- 67) Schwab RJ, Gefter WB, Pack AI, Hoffman EA. Dynamic imaging of the upper airway during respiration in normal subjects. *J Appl Physiol (1985).* 1993 Apr; 74(4):1504-14. PMID: 8514663.
- 68) Schwab RJ, Pack AI, Gupta KB, et al. Upper airway and soft tissue structural changes induced by CPAP in normal subjects. *Am J Respir Crit Care Med.* 1996 Oct; 154(4 Pt 1):1106-16. PMID: 8887615. <https://dx.doi.org/10.1164/ajrccm.154.4.8887615>.
- 69) Pevernagie DA, Stanson AW, Sheedy PF 2nd, et al. Effects of body position on the upper airway of patients with obstructive sleep apnea. *Am J Respir Crit Care Med.* 1995 Jul; 152(1):179-85. PMID: 7599821. <https://dx.doi.org/10.1164/ajrccm.152.1.7599821>.
- 70) Martin SE, Mathur R, Marshall I, Douglas NJ. The effect of age, sex, obesity and posture on upper airway size. *Eur Respir J.* 1997 Sep; 10(9):2087-90. PMID: 9311508. <https://doi.org/10.1183/09031936.97.10092087>.
- 71) Mathru M, Esch O, Lang J, et al. Magnetic resonance imaging of the upper airway. Effects of propofol anesthesia and nasal continuous positive airway pressure in humans. *Anesthesiology.* 1996 Feb; 84(2): 273-9. PMID: 8602656. <https://doi.org/10.1097/00000542-199602000-00004>.
- 72) Montravers P, Dureuil B, Molliex S, Desmonts JM. Effects of intravenous midazolam on the work of breathing. *Anesth Analg.* 1994 Sep; 79(3):558-62. PMID: 8067564. <https://doi.org/10.1213/00000539-199409000-00027>.
- 73) Lam KK, Kunder S, Wong J, et al. Obstructive sleep apnea, pain, and opioids: is the riddle solved? *Curr Opin Anaesthesiol.* 2016 Feb; 29(1):134-40. PMID: 26545144. PMCID: PMC4927322. <https://dx.doi.org/10.1097/ACO.0000000000000265>.
- 74) Shin CH, Zaremba S, Devine S, et al. Effects of obstructive sleep apnoea risk on postoperative respiratory complications: protocol for a hospital-based registry study. *BMJ Open.* 2016 Jan 13; 6(1):e008436. PMID: 26769778. PMCID: PMC4735131. <https://dx.doi.org/10.1136/bmjopen-2015-008436>.
- 75) Yue HJ, Guilleminault C. Opioid medication and sleep-disordered breathing. *Med Clin North Am.* 2010 May; 94(3):435-46. PMID: 20451025. <https://dx.doi.org/10.1016/j.mcna.2010.02.007>.
- 76) Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol (1985).* 2010 Jan; 108(1):206-11. PMID: 19875713. <https://dx.doi.org/10.1152/japplphysiol.00694.2009>.
- 77) Eichenberger A, Proietti S, Wicky S, et al. Morbid obesity and post-operative pulmonary atelectasis: an underestimated problem. *Anesth Analg.* 2002 Dec; 95(6):1788-92, table of contents. PMID: 12456460. <https://doi.org/10.1097/00000539-200212000-00060>.
- 78) Collins LC, Hoberty PD, Walker JF, et al. The effect of body fat distribution on pulmonary function tests. *Chest.* 1995 May; 107(5): 1298-302. PMID: 7750322. <https://doi.org/10.1378/chest.107.5.1298>.
- 79) Biring MS, Lewis MI, Liu JT, Mohsenifar Z. Pulmonary physiologic changes of morbid obesity. *Am J Med Sci.* 1999 Nov; 318(5):293-7. PMID: 10555090. [https://doi.org/10.1016/s0002-9629\(15\)40641-x](https://doi.org/10.1016/s0002-9629(15)40641-x).
- 80) Kress JP, Pohlman AS, Alverdy J, Hall JB. The impact of morbid obesity on oxygen cost of breathing (VO_{2RESP}) at rest. *Am J Respir Crit Care Med.* 1999 Sep; 160(3):883-6. PMID: 10471613. <https://dx.doi.org/10.1164/ajrccm.160.3.9902058>.
- 81) Canoy D, Luben R, Welch A, et al. Abdominal obesity and respiratory function in men and women in the EPIC-Norfolk Study, United Kingdom. *Am J Epidemiol.* 2004 Jun 15; 159(12):1140-9. PMID: 15191931. <https://dx.doi.org/10.1093/aje/kwh155>.
- 82) Thomas PS, Cowen ER, Hulands G, Milledge JS. Respiratory function in the morbidly obese before and after weight loss. *Thorax.* 1989 May; 44(5):382-6. PMID: 2503905. PMCID: PMC461837. <https://doi.org/10.1136/thx.44.5.382>.
- 83) Piper AJ, Grunstein RR. Big breathing: the complex interaction of obesity, hypoventilation, weight loss, and respiratory function. *J Appl Physiol (1985).* 2010 Jan; 108(1):199-205. PMID: 19875712. <https://dx.doi.org/10.1152/japplphysiol.00713.2009>.
- 84) Parameswaran K, Todd DC, Soth M. Altered respiratory physiology in obesity. *Can Respir J.* 2006 May-Jun; 13(4):203-10. PMID: 16779465. PMCID: PMC2683280. <https://doi.org/10.1155/2006/834786>.
- 85) Forrest AL. Buprenorphine and lorazepam. *Anaesthesia.* 1983 Jun; 38(6):598. PMID: 6135366. <https://doi.org/10.1111/j.1365-2044.1983.tb14083.x>.
- 86) Faroqui MH, Cole M, Curran J. Buprenorphine, benzodiazepines and respiratory depression. *Anaesthesia.* 1983 Oct; 38(10):1002-3. PMID: 6139041. <https://doi.org/10.1111/j.1365-2044.1983.tb12045.x>.
- 87) Webster LR. Considering the risks of benzodiazepines and opioids together. *Pain Med.* 2010 Jun; 11(6):801-2. PMID: 20624235. <https://dx.doi.org/10.1111/j.1526-4637.2010.00873.x>.
- 88) Gudin JA, Mogali S, Jones JD, Comer SD. Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. *Postgrad Med.* 2013 Jul; 125(4):115-30. PMID: 23933900. PMCID: PMC4057040. <https://dx.doi.org/10.3810/pgm.2013.07.2684>.
- 89) Goodman JM, Bischel MD, Wagers PW, Barbour BH. Barbiturate intoxication. Morbidity and mortality. *West J Med.* 1976 Mar; 124(3): 179-86. PMID: 1258466. PMCID: PMC1129997.
- 90) Sahn SA, Lakshminarayan S, Pierson DJ, Weil JV. Effect of ethanol on the ventilatory responses to oxygen and carbon dioxide in man. *Clin Sci Mol Med.* 1975 Jul; 49(1):33-8. PMID: 1149393. <https://doi.org/10.1042/cs0490033>.
- 91) Bailey PL, Pace NL, Ashburn MA, et al. Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. *Anesthesiology.* 1990 Nov; 73(5):826-30. PMID: 2122773. <https://doi.org/10.1097/00000542-199011000-00005>.
- 92) Giummarru MJ, Gibson SJ, Allen AR, et al. Polypharmacy and chronic pain: harm exposure is not all about the opioids. *Pain Med.* 2015 Mar; 16(3):472-9. PMID: 25280054. <https://dx.doi.org/10.1111/pme.12586>.
- 93) Jones CM, Paulozzi LJ, Mack KA; Centers for Disease Control and Prevention (CDC). Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths - United States, 2010. *MMWR Morb Mortal Wkly Rep.* 2014 Oct 10; 63(40):881-5. PMID: 25299603.
- 94) Lee HY, Li JH, Wu LT, et al. Survey of methadone-drug interactions among patients of methadone maintenance treatment program in Taiwan. *Subst Abuse Treat Prev Policy.* 2012 Mar 20; 7:11. PMID: 22429858. PMCID: PMC3373376. <https://doi.org/10.1186/1747-597X-7-11>.

- 95) Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug Alcohol Depend.* 2012 Sep 1; 125(1-2):8-18. PMID: 22857878. PMCID: PMC3454351. <https://dx.doi.org/10.1016/j.drugalcdep.2012.07.004>.
- 96) Fields MD, Abate MA, Hu L, et al. Parent and metabolite opioid drug concentrations in unintentional deaths involving opioid and benzodiazepine combinations. *J Forensic Sci.* 2015 Jul; 60(4):950-6. PMID: 26223761. PMCID: PMC4944848. <https://dx.doi.org/10.1111/1556-4029.12807>.
- 97) Wilson KC, Saukkonen JJ. Acute respiratory failure from abused substances. *J Intensive Care Med.* 2004 Jul-Aug; 19(4):183-93. PMID: 15296619. <https://dx.doi.org/10.1177/088506604263918>.
- 98) Pearson J, Poklis J, Poklis A, et al. Postmortem toxicology findings of acetyl fentanyl, fentanyl, and morphine in heroin fatalities in Tampa, Florida. *Acad Forensic Pathol.* 2015 Dec; 5(4):676-89. <https://doi.org/10.23907/2015.072>.
- 99) Sorg MH, Long DL, Abate MA, et al. Additive effects of co-intoxicants in single-opioid induced deaths. *Acad Forensic Pathol.* 2016 Sep; 6(3):532-42. <https://doi.org/10.23907/2016.053>.
- 100) Davis GG; National Association of Medical Examiners and American College of Medical Toxicology Expert Panel on Evaluating and Reporting Opioid Deaths. Recommendations for the investigation, diagnosis, and certification of deaths related to opioid drugs. *Acad Forensic Pathol.* 2013 Mar; 3(1):62-76. <https://doi.org/10.23907/2013.010>,
- 101) Dolinak D. Forensic toxicology: a physiologic perspective. Calgary: Academic Forensic Pathology Inc.; 2013. 480 p.
- 102) Mitler MM, Dawson A, Henriksen SJ, et al. Bedtime ethanol increases resistance of upper airways and produces sleep apneas in asymptomatic snorers. *Alcohol Clin Exp Res.* 1988 Dec; 12(6):801-5. PMID: 3064641. PMCID: PMC2336897. <https://doi.org/10.1111/j.1530-0277.1988.tb01349.x>.
- 103) Dawson A, Bigby BG, Poceta JS, Mitler MM. Effect of bedtime alcohol on inspiratory resistance and respiratory drive in snoring and nonsnoring men. *Alcohol Clin Exp Res.* 1997 Apr; 21(2):183-90. PMID: 9113250. <https://doi.org/10.1097/00000374-199704000-00001>.
- 104) Ali NA, Marshall RW, Allen EM, et al. Comparison of the effects of therapeutic doses of meptazinol and a dextropropoxyphene/paracetamol mixture alone and in combination with ethanol on ventilatory function and saccadic eye movements. *Br J Clin Pharmacol.* 1985 Dec; 20(6):631-7. PMID: 4091995. PMCID: PMC1400831. <https://doi.org/10.1111/j.1365-2125.1985.tb05121.x>.
- 105) Montravers P, Dureuil B, Desmonts JM. Effects of i.v. midazolam on upper airway resistance. *Br J Anaesth.* 1992 Jan; 68(1):27-31. PMID: 1739562. <https://doi.org/10.1093/bja/68.1.27>.
- 106) Duarte R, McNeill A, Drummond G, Tiplady B. Comparison of the sedative, cognitive, and analgesic effects of nitrous oxide, sevoflurane, and ethanol. *Br J Anaesth.* 2008 Feb; 100(2):203-10. PMID: 18211994. <https://dx.doi.org/10.1093/bja/aem369>.
- 107) Davis GG; National Association of Medical Examiners and American College of Medical Toxicology Expert Panel on Evaluating and Reporting Opioid Deaths. National Association of Medical Examiners position paper: recommendations for the investigation, diagnosis, and certification of deaths related to opioid drugs. *Acad Forensic Pathol.* 2013 Mar; 3(1):77-83. <https://doi.org/10.23907/2013.011>.
- 108) Merrill EL, Kariminia A, Binswanger IA, et al. Meta-analysis of drug-related deaths soon after release from prison. *Addiction.* 2010 Sep; 105(9):1545-54. PMID: 20579009. PMCID: PMC2955973. <https://dx.doi.org/10.1111/j.1360-0443.2010.02990.x>.
- 109) Binswanger IA, Blatchford PJ, Mueller SR, Stern MF. Mortality after prison release: opioid overdose and other causes of death, risk factors, and time trends from 1999 to 2009. *Ann Intern Med.* 2013 Nov 5; 159(9):592-600. PMID: 24189594. PMCID: PMC5242316. <https://dx.doi.org/10.7326/0003-4819-159-9-201311050-00005>.
- 110) Binswanger IA, Nowels C, Corsi KF, et al. Return to drug use and overdose after release from prison: a qualitative study of risk and protective factors. *Addict Sci Clin Pract.* 2012; 7:3. PMID: 22966409. PMCID: PMC3414824. <https://dx.doi.org/10.1186/1940-0640-7-3>.
- 111) Takase I, Koizumi T, Fujimoto I, et al. An autopsy case of acetyl fentanyl intoxication caused by insufflation of 'designer drugs'. *Leg Med (Tokyo).* 2016 Jul; 21:38-44. PMID: 27497332. <https://dx.doi.org/10.1016/j.legalmed.2016.05.006>.
- 112) Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA.* 2008 Dec 10; 300(22):2613-20. PMID: 19066381. <https://dx.doi.org/10.1001/jama.2008.802>.
- 113) Sauber-Schatz EK, Mack KA, Diekman ST, Paulozzi LJ. Associations between pain clinic density and distributions of opioid pain relievers, drug-related deaths, hospitalizations, emergency department visits, and neonatal abstinence syndrome in Florida. *Drug Alcohol Depend.* 2013 Nov 1; 133(1):161-6. PMID: 23769424. <https://dx.doi.org/10.1016/j.drugalcdep.2013.05.017>.
- 114) Algren DA, Monteith CP, Punja M, et al. Fentanyl-associated fatalities among illicit drug users in Wayne County, Michigan (July 2005-May 2006). *J Med Toxicol.* 2013 Mar; 9(1):106-15. PMID: 23359211. PMCID: PMC3576499. <https://dx.doi.org/10.1007/s13181-012-0285-4>.
- 115) George AV, Lu JJ, Pisano MV, et al. Carfentanil—an ultra potent opioid. *Am J Emerg Med.* 2010 May; 28(4):530-2. PMID: 20466249. <https://dx.doi.org/10.1016/j.ajem.2010.03.003>.
- 116) Cunningham SM, Haikal NA, Kranner JC. Fatal intoxication with acetyl fentanyl. *J Forensic Sci.* 2016 Jan; 61 Suppl 1:S276-80. PMID: 26389815. <https://dx.doi.org/10.1111/1556-4029.12953>.
- 117) McIntyre IM, Trochta A, Gary RD, et al. An acute butyr-fentanyl fatality: a case report with postmortem concentrations. *J Anal Toxicol.* 2016 Mar; 40(2):162-6. PMID: 26683128. <https://dx.doi.org/10.1093/jat/bkv138>.
- 118) Fort C, Curtis B, Nichols C, Niblo C. Acetyl fentanyl toxicity: two case reports. *J Anal Toxicol.* 2016 Nov; 40(9):754-757. PMID: 27416837. <https://dx.doi.org/10.1093/jat/bkw068>.
- 119) Poklis J, Poklis A, Wolf C, et al. Postmortem tissue distribution of acetyl fentanyl, fentanyl and their respective nor-metabolites analyzed by ultrahigh performance liquid chromatography with tandem mass spectrometry. *Forensic Sci Int.* 2015 Dec; 257:435-41. PMID: 26583960. PMCID: PMC4879818. <https://dx.doi.org/10.1016/j.forsciint.2015.10.021>.
- 120) McIntyre IM, Trochta A, Gary RD, et al. An acute acetyl fentanyl fatality: a case report with postmortem concentrations. *J Anal Toxicol.* 2015 Jul-Aug; 39(6):490-4. PMID: 25917447. <https://dx.doi.org/10.1093/jat/bkv043>.
- 121) Lozier MJ, Boyd M, Stanley C, et al. Acetyl fentanyl, a novel fentanyl analog, causes 14 overdose deaths in Rhode Island, March-May 2013. *J Med Toxicol.* 2015 Jun; 11(2):208-17. PMID: 25934111. PMCID: PMC4469714. <https://dx.doi.org/10.1007/s13181-015-0477-9>.
- 122) Stogner JM. The potential threat of acetyl fentanyl: legal issues, contaminated heroin, and acetyl fentanyl "disguised" as other opioids. *Ann Emerg Med.* 2014 Dec; 64(6):637-9. PMID: 25153008. <https://dx.doi.org/10.1016/j.annemergmed.2014.07.017>.
- 123) Pattinson KT. Opioids and the control of respiration. *Br J Anaesth.* 2008 Jun; 100(6):747-58. PMID: 1845664. <https://dx.doi.org/10.1093/bja/aen094>.

- 124) Walsh JH, Maddison KJ, Platt PR, et al. Influence of head extension, flexion, and rotation on collapsibility of the passive upper airway. *Sleep*. 2008 Oct; 31(10):1440-7. PMID: 18853942. PMCID: PMC2572750.
- 125) Dinis-Oliveira RJ, Santos A, Magalhães T. "Foam Cone" exuding from the mouth and nostrils following heroin overdose. *Toxicol Mech Methods*. 2012 Feb; 22(2):159-60. PMID: 22242632. <https://dx.doi.org/10.3109/15376516.2011.610388>.
- 126) Naso-Kaspar CK, Herndon GW, Wyman JF, et al. 'Lingering' opiate deaths? Concentration of opiates in medulla and femoral blood. *J Anal Toxicol*. 2013 Oct; 37(8):507-11. PMID: 23869071. <https://dx.doi.org/10.1093/jat/bkt061>.
- 127) Sternbach G. William Osler: narcotic-induced pulmonary edema. *J Emerg Med*. 1983; 1(2):165-7. PMID: 6389671. [https://doi.org/10.1016/0736-4679\(83\)90052-5](https://doi.org/10.1016/0736-4679(83)90052-5).
- 128) Helpman M, Rho YM. Deaths from narcotism in New York City. Incidence, circumstances, and postmortem findings. *N Y State J Med*. 1966 Sep 15; 66(18):2391-408. PMID: 5222195.
- 129) Sterrett C, Brownfield J, Korn CS, et al. Patterns of presentation in heroin overdose resulting in pulmonary edema. *Am J Emerg Med*. 2003 Jan; 21(1):32-4. PMID: 12563576. <https://dx.doi.org/10.1053/ajem.2003.50006>.
- 130) Duberstein JL, Kaufman DM. A clinical study of an epidemic of heroin intoxication and heroin-induced pulmonary edema. *Am J Med*. 1971 Dec; 51(6):704-14. PMID: 5129541. [https://doi.org/10.1016/0002-9343\(71\)90298-1](https://doi.org/10.1016/0002-9343(71)90298-1).
- 131) Silber R, Clerkin EP. Pulmonary edema in acute heroin poisoning: report of four cases. *Am J Med*. 1959 Jul; 27(1):187-92. PMID: 13661202. [https://doi.org/10.1016/0002-9343\(59\)90075-0](https://doi.org/10.1016/0002-9343(59)90075-0).
- 132) Troen P. Pulmonary edema in acute opium intoxication. *N Engl J Med*. 1953 Feb 26; 248(9):364-6. PMID: 13025699. <https://dx.doi.org/10.1056/NEJM195302262480903>.
- 133) Motley HL, Cournand A, et al. The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. *Am J Physiol*. 1947 Aug; 150(2):315-20. PMID: 20258388.
- 134) Dehnert C, Risse F, Ley S, et al. Magnetic resonance imaging of uneven pulmonary perfusion in hypoxia in humans. *Am J Respir Crit Care Med*. 2006 Nov 15; 174(10):1132-8. PMID: 16946125. <https://doi.org/10.1164/rccm.200606-780oc>.
- 135) Swenson ER. Hypoxic pulmonary vasoconstriction. *High Alt Med Biol*. 2013 Jun; 14(2):101-10. PMID: 23795729.
- 136) Grunig E, Mereles D, Hildebrandt W, et al. Stress Doppler echocardiography for identification of susceptibility to high altitude pulmonary edema. *J Am Coll Cardiol*. 2000 Mar 15; 35(4):980-7. PMID: 10732898. [https://doi.org/10.1016/s0735-1097\(99\)00633-6](https://doi.org/10.1016/s0735-1097(99)00633-6).
- 137) West JB, Tsukimoto K, Mathieu-Costello O, Prediletto R. Stress failure in pulmonary capillaries. *J Appl Physiol (1985)*. 1991 Apr; 70(4):1731-42. PMID: 2055852.
- 138) Hsiao PN, Chang MC, Cheng WF, et al. Morphine induces apoptosis of human endothelial cells through nitric oxide and reactive oxygen species pathways. *Toxicology*. 2009 Feb 4; 256(1-2):83-91. PMID: 19070643. <https://doi.org/10.1016/j.tox.2008.11.015>.
- 139) Liu HC, Anday JK, House SD, Chang SL. Dual effects of morphine on permeability and apoptosis of vascular endothelial cells: morphine potentiates lipopolysaccharide-induced permeability and apoptosis of vascular endothelial cells. *J Neuroimmunol*. 2004 Jan; 146(1-2):13-21. PMID: 14698842. <https://doi.org/10.1016/j.jneuroim.2003.09.016>.
- 140) Dettmeyer R, Schmidt P, Musshoff F, Dreisvogt C, Madea B. Pulmonary edema in fatal heroin overdose: immunohistological investigations with IgE, collagen IV and laminin - no increase of defects of alveolar-capillary membranes. *Forensic Sci Int*. 2000 May 15; 110(2):87-96. PMID: 10808097. [https://doi.org/10.1016/s0379-0738\(00\)00148-1](https://doi.org/10.1016/s0379-0738(00)00148-1).
- 141) Yamanaka T, Sadikot RT. Opioid effect on lungs. *Respirology*. 2013 Feb; 18(2):255-62. PMID: 23066838. <https://doi.org/10.1111/j.1440-1843.2012.02307.x>.
- 142) Bhattacharya M, Kallet RH, Ware LB, Matthay MA. Negative-pressure pulmonary edema. *Chest*. 2016 Oct; 150(4):927-933. PMID: 27063348. <https://doi.org/10.1016/j.chest.2016.03.043>.
- 143) Lemyze M, Mallat J. Understanding negative pressure pulmonary edema. *Intensive Care Med*. 2014 Aug; 40(8):1140-3. PMID: 24797685. <https://doi.org/10.1007/s00134-014-3307-7>.
- 144) Fineschi V, Cecchi R, Centini F, Reattelli LP, Turillazzi E. Immunohistochemical quantification of pulmonary mast-cells and post-mortem blood dosages of tryptase and eosinophil cationic protein in 48 heroin-related deaths. *Forensic Sci Int*. 2001 Sep 1; 120(3):189-94. PMID: 11473801. [https://doi.org/10.1016/s0379-0738\(00\)00469-2](https://doi.org/10.1016/s0379-0738(00)00469-2).
- 145) Edston E, van Hage-Hamsten M. Anaphylactoid shock--a common cause of death in heroin addicts? *Allergy*. 1997 Sep; 52(9):950-4. PMID: 9298181. <https://doi.org/10.1111/j.1398-9995.1997.tb01256.x>.
- 146) Rosow CE, Moss J, Philbin DM, Savarese JJ. Histamine release during morphine and fentanyl anesthesia. *Anesthesiology*. 1982 Feb; 56(2):93-6. PMID: 6172999. <https://doi.org/10.1097/00000542-198202000-00003>.
- 147) Philbin DM, Moss J, Akins CW, et al. The use of H1 and H2 histamine antagonists with morphine anesthesia: a double-blind study. *Anesthesiology*. 1981 Sep; 55(3):292-6. PMID: 6115596. <https://doi.org/10.1097/00000542-198109000-00019>.
- 148) Withington DE, Patrick JA, Reynolds F. Histamine release by morphine and diamorphine in man. *Anesthesia*. 1993 Jan; 48(1):26-9. PMID: 7679560. <https://doi.org/10.1111/j.1365-2044.1993.tb06785.x>.
- 149) Saucedo R, Erill S. Morphine-induced skin wheals: a possible model for the study of histamine release. *Clin Pharmacol Ther*. 1985 Oct; 38(4):365-70. PMID: 2412748. <https://doi.org/10.1038/clpt.1985.189>.
- 150) Hermens JM, Ebertz JM, Hanifin JM, Hirshman CA. Comparison of histamine release in human skin mast cells induced by morphine, fentanyl, and oxymorphone. *Anesthesiology*. 1985 Feb; 62(2):124-9. PMID: 2578752. <https://doi.org/10.1097/00000542-198502000-00005>.
- 151) Fahmy NR, Sunder N, Soter NA. Role of histamine in the hemodynamic and plasma catecholamine responses to morphine. *Clin Pharmacol Ther*. 1983 May; 33(5):615-20. PMID: 6839633. <https://doi.org/10.1038/clpt.1983.83>.
- 152) Fahmy NR. Hemodynamics, plasma histamine, and catecholamine concentrations during an anaphylactoid reaction to morphine. *Anesthesiology*. 1981 Sep; 55(3):329-31. PMID: 7270959. <https://doi.org/10.1097/00000542-198109000-00028>.
- 153) Suzuki A, Ishihara H, Hashiba E, et al. Detection of histamine-induced capillary protein leakage and hypovolaemia by determination of indocyanine green and glucose dilution method in dogs. *Intensive Care Med*. 1999 Mar; 25(3):304-10. PMID: 10229166. <https://doi.org/10.1007/s001340050840>.
- 154) Bhargava KP, Nath R, Palit G. Nature of histamine receptors concerned in capillary permeability. *Br J Pharmacol*. 1977 Feb; 59(2): 349-51. PMID: 837022. <https://doi.org/10.1111/j.1476-5381.1977.tb07499.x>.



- 155) Baker CH. Nonhemodynamic effects of histamine on gracilis muscle capillary permeability. *J Pharmacol Exp Ther.* 1979 Dec; 211(3):672-7. PMID: 512930.
- 156) Haraldsson B, Zackrisson U, Rippe B. Calcium dependence of histamine-induced increases in capillary permeability in isolated perfused rat hindquarters. *Acta Physiol Scand.* 1986 Oct; 128(2):247-58. PMID: 3776648. <https://doi.org/10.1111/j.1748-1716.1986.tb07973.x>.
- 157) Meyrick B, Brigham KL. Increased permeability associated with dilatation of endothelial cell junctions caused by histamine in intimal explants from bovine pulmonary artery. *Exp Lung Res.* 1984; 6(1):11-25. PMID: 6376082. <https://doi.org/10.3109/01902148409087892>.
- 158) Konstantinova SV, Normann PT, Arnestad M, et al. Morphine to codeine concentration ratio in blood and urine as a marker of illicit heroin use in forensic autopsy samples. *Forensic Sci Int.* 2012 Apr 10; 217(1-3):216-21. PMID: 22137531. <https://doi.org/10.1016/j.forsciint.2011.11.007>.
- 159) Jones AW, Holmgren A. Concentration ratios of free-morphine to free-codeine in femoral blood in heroin-related poisoning deaths. *Leg Med (Tokyo).* 2011 Jul; 13(4):171-3. PMID: 21377914. <https://doi.org/10.1016/j.legalmed.2011.02.002>.
- 160) Ceder G, Jones AW. Concentration ratios of morphine to codeine in blood of impaired drivers as evidence of heroin use and not medication with codeine. *Clin Chem.* 2001 Nov; 47(11):1980-4. PMID: 11673366.
- 161) Moriya F, Chan KM, Hashimoto Y. Concentrations of morphine and codeine in urine of heroin abusers. *Leg Med (Tokyo).* 1999 Sep; 1(3):140-4. PMID: 12935484. [https://doi.org/10.1016/s1344-6223\(99\)80026-1](https://doi.org/10.1016/s1344-6223(99)80026-1).
- 162) Klausner JM, Caspi J, Lelcuk S, et al. Delayed muscular rigidity and respiratory depression following fentanyl anesthesia. *Arch Surg.* 1988 Jan; 123(1):66-7. PMID: 3337659.
- 163) Gill JR, Lin PT, Nelson L. Reliability of postmortem fentanyl concentrations in determining the cause of death. *J Med Toxicol.* 2013 Mar; 9(1):34-41. PMID: 22890811. <https://doi.org/10.1007/s13181-012-0253-z>.
- 164) Smith HS. Opioid metabolism. *Mayo Clin Proc.* 2009 Jul; 84(7):613-24. [https://doi.org/10.1016/s0025-6196\(11\)60750-7](https://doi.org/10.1016/s0025-6196(11)60750-7).
- 165) Smith HS. The metabolism of opioid agents and the clinical impact of their active metabolites. *Clin J Pain.* 2011 Nov-Dec; 27(9):824-38. PMID: 21677572. <https://doi.org/10.1097/ajp.0b013e31821d8ac1>.
- 166) Coller JK, Christrup LL, Somogyi AA. Role of active metabolites in the use of opioids. *Eur J Clin Pharmacol.* 2009; 65(2):121-39. <https://doi.org/10.1007/s00228-008-0570-y>.



Emerging Synthetic Fentanyl Analogs

Harold E. Schueler

ABSTRACT

Hundreds of synthetic substances have been introduced into the illicit drug market over the last ten years, but none of these drugs has had as poisonous a consequence as the emergence of the synthetic fentanyl analogs. Initially, pharmaceutical grade or illicit fentanyl was mixed with heroin, allegedly to boost the potency of the heroin. Then, the amounts of fentanyl spiked gradually increased until the proportion of fentanyl was greater than the proportion of heroin. Ultimately, many overdose cases began consisting of only fentanyl. The emergence of numerous synthetic fentanyl analogs, including acetylfentanyl, butyrylfentanyl, acrylfentanyl, furanylfentanyl and β -hydroxythiofentanyl, which are manufactured in China, were made available to the illicit drug traffickers over the Internet. In July of 2016, the most potent commercially available opioid, carfentanil, started appearing in illicit drug submissions and medical examiner death investigation cases in Northeast Ohio. Postmortem femoral blood carfentanil concentrations are in the picogram per milliliter (pg/mL) range, which is extremely low, and tests the limits of detection for most analytical forensic toxicology laboratories. The interpretation of these low carfentanil blood concentrations in antemortem and postmortem specimens is made difficult due to the overlap in the concentrations between these specimen types. The presence of these powerful synthetic fentanyl analogs presents a challenge to forensic toxicology laboratories preparing to analyze for these substances. *Acad Forensic Pathol.* 2017 7(1): 36-40

AUTHOR

Harold E. Schueler PhD, Cuyahoga County Medical Examiner's Office - Toxicology

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, general supervision, writing assistance and/or technical editing.

CORRESPONDENCE

Harold E. Schueler PhD, 11001 Cedar Avenue, Cleveland OH 44106-3043, hschueler@cuyahogacounty.us

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The author, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The author has indicated that he does not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Fentanyl analogs, Carfentanil, Synthetic opioids, 3-methylfentanyl

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.004>

Submitted for consideration on 9 Jan 2017. Accepted for publication on 30 Jan 2017

INTRODUCTION

During the past decade, several hundreds of synthetic compounds that are manufactured to mimic the pharmacology of various illegal drug classes (e.g., cannabinoids, cathinones, hallucinogens, opioids) have been introduced into the illicit drug market. None of these groups of substances have had as significant an impact on drug overdose deaths as the synthetic fentanyl analogs. In Cuyahoga County, Ohio, the heroin detected in drug paraphernalia and autopsy specimens was initially mixed with either pharmaceutical grade or illicit fentanyl, presumably in order to boost the potency of the heroin. Over time, the amount of fentanyl spiked gradually increased until the proportion of fentanyl became greater than the proportion of heroin. Eventually, many of the overdose death cases consisted only of fentanyl. Subsequently, numerous synthetic fentanyl analogs were being manufactured in China, and these highly potent drugs were made available to the illicit drug traffickers over the Internet. In 2016, one of the most potent commercially available opioids, carfentanil (Wildnil, a large animal general anesthetic agent) was being produced and started appearing in illicit drug submissions and medical examiner death investigation cases throughout Northeastern Ohio. The emergence of these powerful synthetic fentanyl analogs has directed attention to some deficiencies in laboratory drug testing that hinder forensic toxicology laboratories preparing to analyze for these compounds.

DISCUSSION

Fentanyl was first synthesized by Paul Janssen in 1960 and the extensive use of the drug prompted the production of the citrate salt (Sublimaze), which quickly gained popularity as a general anesthetic in medicine. Fentanyl being a strong mu-opioid receptor agonist with rapid onset and short duration of action, is used as a potent synthetic opioid analgesic for the treatment of moderate to severe chronic pain. The syntheses of other legitimate fentanyl analogs also possessing rapid onset and short duration of action, such as sufentanil in 1974 and alfentanil in 1976 by Janssen Pharmaceutica, and remifentanil in 1996 by Glaxo Welcome, pro-

vided medical professionals with several options for potent, short-acting synthetic opioid analgesics that offer pain relief to patients during surgery and as an adjunct to anesthesia. Until the mid-1990s, only occasional fentanyl or fentanyl analog overdoses were reported. Most of these opioid overdose cases involved either medical misuse or the abuse of fentanyl or one of the potent synthetic analogs by medical professionals having access to these drugs. However, during a five-month period in 1988, at least 16 overdose deaths were attributed to the extremely potent 3-methylfentanyl analog ("China White"), which was synthesized by an industrial chemist in Pittsburgh (1, 2). The drug was only distributed locally and most of the deaths occurred during the several months of investigation by local and federal law enforcement agencies. The abuse of pharmaceutical grade fentanyl by the public increased after the drug was released in the 1990s as a transdermal patch for mild to severe chronic pain relief. Since then, thousands of overdose deaths have resulted from the illicit misuse by self-administering multiple patches simultaneously or using nontransdermal modes of administration compromising the contents of the fentanyl patch, such as intravenous, oral or transmucosal, rectal, or inhalation of the drug (3-8).

More recently, heroin laced with fentanyl was being distributed and was determined to be responsible for at least 700 deaths nationwide between 2013 and 2014 (9). To be more competitive, drug traffickers were adding either pharmaceutical grade or illicit fentanyl with the heroin in order to increase the potency or compensate for lower quality heroin. Routine postmortem toxicological analyses on blood specimens obtained from these deaths frequently detected the metabolites of heroin (i.e., morphine, codeine, and 6-acetylmorphine), fentanyl, N-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP), and N-(1-Phenethylpiperidin-4-yl)-N-phenylacetamide (acetylfentanyl). The 4-ANPP has been designated by the Drug Enforcement Administration (DEA) as an intermediate chemical precursor used in the synthesis process for the illicit production of the schedule II controlled substance, fentanyl, and other related opioids. Accordingly, the DEA approved the control of 4-ANPP also as a schedule II substance under the Controlled Sub-

stances Act (CSA). The presence of a small amount of 4-ANPP detected in a postmortem specimen may be an indication that the fentanyl taken was clandestinely manufactured in which trace amounts of 4-ANPP can remain as an impurity. Between 2005 and 2006, approximately 1000 fentanyl-related overdose deaths were the result of illicitly produced fentanyl (10). The 4-ANPP is also suspected to be involved in the production of other fentanyl analog compounds as well, such as acetyl fentanyl, butyryl fentanyl, and furanyl fentanyl. Some investigators believe 4-ANPP may also be a metabolite of fentanyl and these other analogs (11, 12). For certain enzyme-linked immunosorbent assay (ELISA) drug screens, the cross-reactivity for 4-ANPP with the fentanyl assay is very low and will not produce a positive result. Acetyl fentanyl was ruled as a DEA Schedule I substance under the CSA, since the drug has no known approved medical or industrial applications and after 39 acetyl fentanyl overdose deaths occurred in six states during 2013 and 2014 (13). Acetyl fentanyl can be readily converted into fentanyl and is frequently detected as an impurity from the illicit manufacturing of fentanyl. The risk of an acetyl fentanyl overdose is quite high due to the fact that the drug is about 15 times more potent than morphine. Postmortem blood acetyl fentanyl concen-

trations ranged from 1.6 to 2.8 ng/mL from four cases ruled as multiple drug intoxications including fentanyl, heroin, cocaine, and phencyclidine. Acetyl fentanyl is sold over the Internet, where the drug is sometimes posted as a “research chemical.” The cross-reactivity for acetyl fentanyl with the fentanyl assay on most ELISA drug screens is high enough to produce a positive result.

Within the last two years, a barrage of many different fentanyl analogs has been introduced into the illicit drug market including: N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenylfuran-2-carboxamide (furanyl fentanyl); N-(3-methyl-1-phenethyl-4-piperidinyl)-N-phenyl-propanamide (3-methyl fentanyl); N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]pentanamide (valeryl fentanyl); N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenylbutyramide (butyryl fentanyl); N-{1-[2-hydroxy-2-(thiophen-2-yl)ethyl]piperidin-4-yl}-N-phenylpropanamide (β -Hydroxythiofentanyl); N-Phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]prop-2-enamide (acrylfentanyl); and most recently, 4-((1-oxopropyl)-phenylamino)-1-(2-phenylethyl)-4-piperidinecarboxylic acid methyl ester (carfentanil) (**Figure 1**).

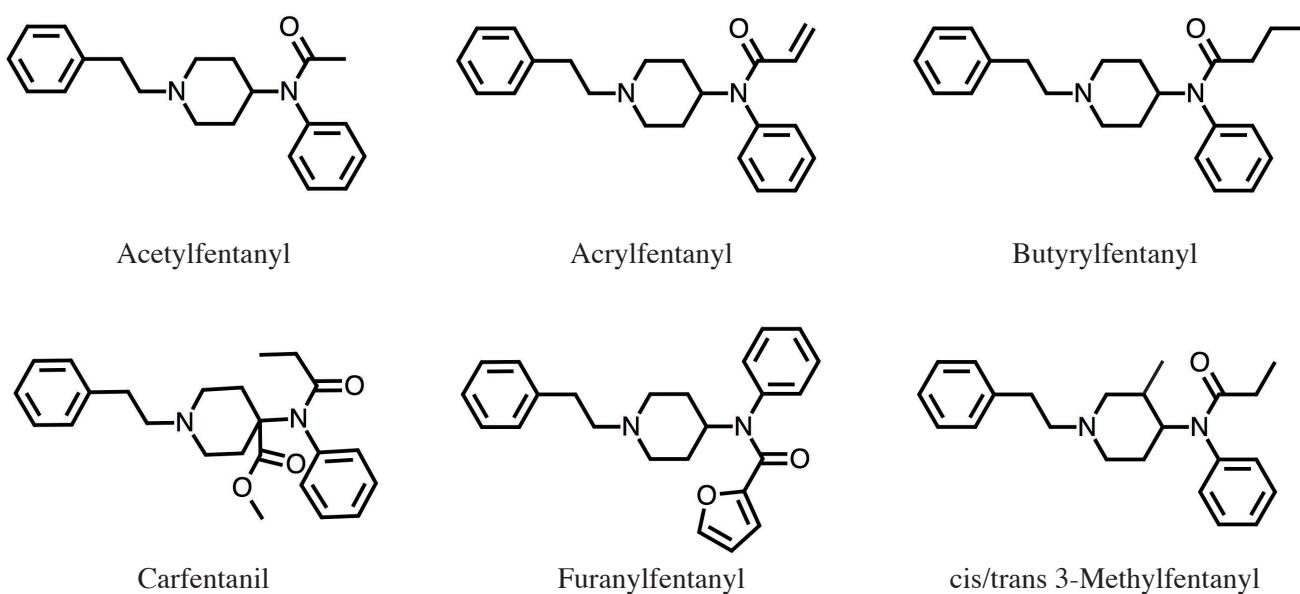


Figure 1: Structures of some fentanyl analogs.

These fentanyl analogs are manufactured in China, sold over the Internet, and enter into the United States through Canada or Mexico. Ohio was hit exceptionally hard in 2016 by the influx of carfentanil with emergency rooms and coroners reporting record-breaking overdose admissions and deaths, respectively (14). Most ELISA fentanyl immunoassays demonstrate positive cross-reactivity with several of the fentanyl derivatives, including furanylfentanyl, butyrylfentanyl and valerylfentanyl. Currently, no fentanyl immunoassay cross-reacts with carfentanil, which requires a specific assay. The relative potency of some of these analogs compared to morphine is shown in **Table 1**.

In Cuyahoga County, an 80-year-old male who died at the hospital of a 3-methylfentanyl overdose had an antemortem hospital blood concentration of 1.13 ng/mL 3-methylfentanyl; no other drugs were present. Postmortem femoral blood carfentanil concentrations for ten deaths in Cuyahoga County ranged from 10.7 to 535 pg/mL, with mean and median concentrations of 159 and 95 pg/mL, respectively. In four cases, carfentanil was not detected in the femoral blood; alternate matrices, such as urine or vitreous humor, were analyzed for the presence of the drug. The postmortem urine carfentanil concentration range for 14 cases was from 14.5 to 6842 pg/mL, with mean and median concentrations of 1098 and 367 pg/mL, respectively. The two cases involving vitreous humor had 25.2 and 96.8 pg/mL of carfentanil. These very low 3-methylfentanyl and carfentanil concentrations demonstrate the extreme potency of these fentanyl analogs. In some

Table 1: Fentanyl Analog Potencies Relative to Morphine

| Fentanyl Analogs | Compared to Morphine |
|------------------|----------------------------------|
| Fentanyl | 80 to 100x |
| Acetylentanyl | 15x |
| Valerylfentanyl | < 20x |
| Furanylfentanyl | 20x |
| Butyrylfentanyl | 20 to 25x |
| Acrylfentanyl | 100x |
| 3-Methylfentanyl | 400x trans and 6000x cis isomers |
| Carfentanil | 10 000 to 100 000x |

instances, the determination of the cause of death was based solely on the presence of carfentanil in the urine or vitreous humor. Interestingly, six law enforcement “driving under the influence” cases have also been found positive for carfentanil, with antemortem blood concentrations of 11.8, 15.2, 48.4, 100, 220, and 293 pg/mL (mean 114 and median 74 pg/mL). This overlap of antemortem and postmortem carfentanil blood concentrations further complicates the interpretation of nontoxic and toxic carfentanil concentrations.

CONCLUSION

This latest epidemic of synthetic fentanyl analogs has added to the escalating pressure on forensic toxicology laboratories to increase the scope of analytes detected in routine comprehensive drug screens and to improve sensitivity by significantly lowering levels of detection. This comes on the heels of several other outbreaks of synthetic compounds including synthetic cannabinoids, synthetic cathinones, and synthetic phenethylamines that have already negatively impacted many forensic toxicology laboratories. Most standard ELISA drug screens do not adequately detect the majority of synthetic compounds being found in cases. By adding more specific ELISA assays to already large drug screening panels increases the amount of labor, time, and cost necessary to complete these drug-related cases. The limited availability of standard reference materials and the inability to quickly acquire instrumentation that is faster, more comprehensive, and sensitive, such as high performance liquid chromatography/time-of-flight mass spectrometry, are factors affecting the performance of these laboratories. Synthetic fentanyl analogs are the most potent substances to enter the illicit drug market. Only time will tell if these extremely toxic compounds will end drug users’ attraction with lethal highs or fuel the search for more potent, and ultimately deadly, synthetic drugs.

REFERENCES

- 1) Hibbs J, Perper J, Winek CL. An outbreak of designer drug—related deaths in Pennsylvania. *JAMA*. 1991 Feb 27; 265(8):1011-3. PMID: 1867667. <https://doi.org/10.1001/jama.265.8.1011>.
- 2) Ackerman J. China White plan conceived by drug addict. *Pittsburgh Post-Gazette*. 1988 Dec 3; 62(108):1, 6.



- 3) Reeves MD, Ginifer CJ. Fatal intravenous misuse of transdermal fentanyl. *Med J Aust.* 2002 Nov 18; 177(10):552-3. PMID: 12429004.
- 4) Lilleng PK, Mehlum LI, Bachs L, Morild I. Deaths after intravenous misuse of transdermal fentanyl. *J Forensic Sci.* 2004 Nov; 49(6): 1364-6. PMID: 15568716.
- 5) Kramer C, Tawney M. A fatal overdose of transdermally administered fentanyl. *J Am Osteopath Assoc.* 1998 Jul; 98(7):385-6. PMID: 9695458.
- 6) Woodall KL, Martin TL, McLellan BA. Oral abuse of fentanyl patches (Duragesic): seven case reports. *J Forensic Sci.* 2008 Jan; 53(1):222-5. PMID: 18279262. <https://dx.doi.org/10.1111/j.1556-4029.2007.00597.x>.
- 7) Coon TP, Miller M, Kaylor D, Jones-Spangle K. Rectal insertion of fentanyl patches: a new route of toxicity. *Ann Emerg Med.* 2005 Nov; 46(5):473. PMID: 16271683. <https://dx.doi.org/10.1016/j.annemergmed.2005.06.450>.
- 8) Marquardt KA, Tharratt RS. Inhalation abuse of fentanyl patch. *J Toxicol Clin Toxicol.* 1994; 32(1):75-8. PMID: 8308952. <https://doi.org/10.3109/15563659409000433>.
- 9) 2015 National Drug Threat Assessment Summary [Internet]. Springfield (VA): U.S. Drug Enforcement Administration; c2016 [cited 2017 Jan 9]. Fentanyl; . p.42. Available from: <https://www.dea.gov/docs/2015%20NDTA%20Report.pdf>.
- 10) National Forensic Laboratory Information System (NFLIS) special report: Fentanyl, 2003-2006 [Internet]. Washington: U.S. Drug Enforcement Administration; c2008 [cited 2017 Jan 9]. Fentanyl prescriptions dispensed; p. 4. Available from: <https://www.deadiversion.usdoj.gov/nflis/fentanyl.pdf>.
- 11) Labroo RB, Paine MF, Thummel KE, Kharasch ED. Fentanyl metabolism by human hepatic and intestinal cytochrome P450 3A4: implications for interindividual variability in disposition, efficacy, and drug interactions. *Drug Metab Dispos.* 1997 Sep; 25(9):1072-80. PMID: 9311623.
- 12) Melent'ev AB, Kataev SS, Dvorskaya ON. Identification and analytical properties of acetyl fentanyl metabolites. *J Anal Chem.* 2015; 70(2):240-8. <https://doi.org/10.1134/s1061934815020124>.
- 13) Drug Enforcement Administration, Department of Justice. Schedules of controlled substances: temporary placement of acetyl fentanyl into schedule I. Final order. *Fed Regist.* 2015 Jul 17; 80(137):42381-5. PMID: 26189217.
- 14) Schueler, Harold (Cuyahoga County Medical Examiner's Office - Toxicology, Cleveland, OH). Personal conversations with: staff of Summit County (OH) Medical Examiner's Office, Franklin County (OH) Coroner's Office, and Hamilton County (OH) Coroner's Office. 2016.



The Evolution of the Opiate/Opioid Crisis in Cuyahoga County

Thomas P. Gilson, Hugh Shannon, Jaime Freiburger

ABSTRACT

The United States continues to grapple with an epidemic of opiate/opioid drugs. This crisis initially manifested itself in the use and abuse of opioid pain relievers and has since seen an increase in illicit opiate/opioid drug use mortality. Cuyahoga County (metropolitan Cleveland) has been an area where the crisis has been particularly acute; this paper updates our previous experience. Most notable in the evolution of the drug epidemic has been an increase in mortality associated with fentanyl and an alarming rise in overall deaths, largely attributable to the emergence of fentanyl (a 64% increase in total overdose deaths from 2015 to 2016, with fentanyl increasing 324%). Fentanyl is a synthetic opioid with use in medical analgesia and anesthesia; however, most of the current supply is of clandestinely manufactured origin. Also of concern is the recent appearance of illicit fentanyl analogues, which are briefly described in this report. White males continue to be the most frequent overdose victims in the current crisis. A decrease of age appears to have taken place with the emergence of fentanyl with the most common age group being between 30 and 44 years of age. The majority of decedents are nonurban residents. Educationally, most of these decedents have a high school diploma or less schooling and a significant percentage consists of manual laborers. Medical examiners are an important source of information necessary to develop prevention and interdiction strategies. Challenges faced regarding adequate funding, instrumentation, and staffing are being felt. *Acad Forensic Pathol.* 2017 7(1): 41-49

AUTHORS

Thomas P. Gilson MD, Cuyahoga County Regional Forensic Science Laboratory

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, principal investigator of a related study listed in the citations.

Hugh Shannon, Cuyahoga County Medical Examiner's Office

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, general administrative support, writing assistance and/or technical editing.

Jaime Freiburger BS, Cuyahoga County Medical Examiner's Office

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, general administrative support.

CORRESPONDENCE

Thomas P. Gilson MD, 11001 Cedar Avenue, Cleveland OH 44106, docgilson@msn.com

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Heroin, Fentanyl, Opioid, Cocaine, Epidemiology

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.005>

Submitted for consideration on 2 Jan 2017. Accepted for publication on 30 Jan 2017

INTRODUCTION

Many regions of the United States are in the midst of an epidemic of drug-related mortality, largely driven by opiates/opioids (O/O) (1-3). While this crisis appears to have its roots in the overprescribing of opioid pain relievers (OPR), more recent years have seen a transition to illicit narcotics, primarily heroin and fentanyl (4-7). In a previous report, we documented our experience with the heroin epidemic in Cuyahoga County (metropolitan Cleveland) from 2007 through 2012 when this transition began (5). This paper provides an update to that report, with a focus on the evolution of drug abuse and mortality in our community through most of 2016, as the data were available at the time of writing. During this interval, the problem has significantly changed and, unfortunately, worsened greatly. Furthermore, in-depth examination of decremental information is also presented with suggestions as to possible public health interventions based on these data.

METHODS

The Cuyahoga County Medical Examiner's Office (CCMEO) has a statutory responsibility to investigate all deaths that are unnatural, suspicious, or involve the sudden, unexpected death of a person in apparent good health. The possibility of a drug-related cause of death will initiate an investigation by CCMEO. Suspected drug-related deaths (DRD) with little or no medical intervention are transported to the mortuary for full autopsy. Deaths after hospitalization with adequate evaluation (e.g., negative computed tomography of the head) may be viewed with no autopsy. Where possible, toxicology testing on admission samples is conducted by the CCMEO Toxicology Laboratory. After full autopsy with routine histology and toxicology, deaths will be certified as drug-related when the sum of the investigation conducted by a board-certified forensic pathologist supports that determination. Barriers to intentional self-harm or overdose as a result of the direct actions of another person, manner of death is generally ruled accidental.

All DRD in our jurisdiction underwent intensive case

review and from 2011 through the third quarter of 2016 (with full-year projections where appropriate), cases were analyzed for basic demographic information (i.e., age, gender, race) and residency status (i.e., urban vs. suburban). More recent years (2015 and 2016) were also analyzed for education level and occupation based on death certificate entries for these variables. The more recent DRD were further stratified by lethal intoxicant represented by heroin, fentanyl, cocaine, OPR, and all others. In our earlier study, we used oxycodone data as a surrogate for OPR, as this has been the major driver of OPR trends in our region (5). Data presented here include all OPR drugs. Additional analysis for mortality involving fentanyl analogues and U-47700 (a synthetic opioid-like analgesic and Schedule I controlled substance with an approximate potency of 7.5 times that of morphine) was also undertaken; however, this is a relatively small population (thus far) and a very recent development in our jurisdiction so more in-depth characterization has not yet been performed. All DRD were searched in the Ohio Automated Rx Reporting System (OARRS), the state prescription drug monitoring program (PDMP). Access to OARRS was initially granted to CCMEO in 2013, so 2012 data range in "look back" from six to 18 months. Otherwise all retrospective OARRS searches extend up to two years. In mid-2015, reporting to the OARRS system by prescribers and distributors changed from voluntary to mandatory.

RESULTS

Total overdose mortality has increased over the last decade. From 2006 to 2014 (**Figure 1**), the total DRD increased from 250 to 353 (41%). Heroin-associated deaths increased in this time period from 49 to 198 (304%). Fentanyl-associated mortality did not show a significant rise until 2014, when 37 deaths were observed, primarily in the last two months of the year. Deaths associated with OPR and cocaine remained relatively unchanged through this time period. The chart shows total DRD as well as those by a particular associated substance. Each line includes all deaths associated with that individual drug, either alone or in combination with other drugs. However, most fatalities are polysubstance DRD and thus, are included in

more than one line of the chart. Therefore, the categories represented are not mutually exclusive.

In 2015, DRD showed only a modest increase (**Figure 1**) to 370 (5%) and heroin-associated deaths actually declined to 184 (-7%). Of note, however, the number of fentanyl deaths rose sharply to 92 (149%). Projections for 2016 show an acute worsening of the problem with projected increases in DRD (608, 64%), heroin-associated deaths (299, 62%), fentanyl-associated deaths (394, 328%), and cocaine-associated deaths (230, 100%). Rates for OPR have continued to remain relatively stable (**Figure 1**). Drug-related deaths not involving one of these four drugs fell from 47 in 2015 (13% of all DRD) to 20 through the third quarter in 2016 (4% of all DRD). In 2016, fentanyl analogues and U-47700 have been responsible for at least 50 deaths through the first three quarters of the

year (**Table 1**). These drugs were not encountered in 2015. The major analogues seen have been carfentanil and acetyl fentanyl. They are included in the general fentanyl totals for 2016.

Deaths due to cocaine alone (**Table 2**) rose very little from 2015 to 2016 (42 in 2015 to a projection of 61 in 2016) while deaths from heroin alone appear to have fallen from 84 in 2015 to a projection of 57 for 2016 (32%). Deaths associated with fentanyl alone will likely triple from 2015 to 2016 (from 29 to a projection of 95 in 2016) and fentanyl is also present in most of the fatal mixed intoxications involving both heroin and cocaine. In 2016, combined heroin and fentanyl overdoses are projected to rise 343% (to a projected 111 from 25), combined cocaine and fentanyl overdoses by 522% (projected 57, up from just 9), and overdoses with all three present by 214% (pro-

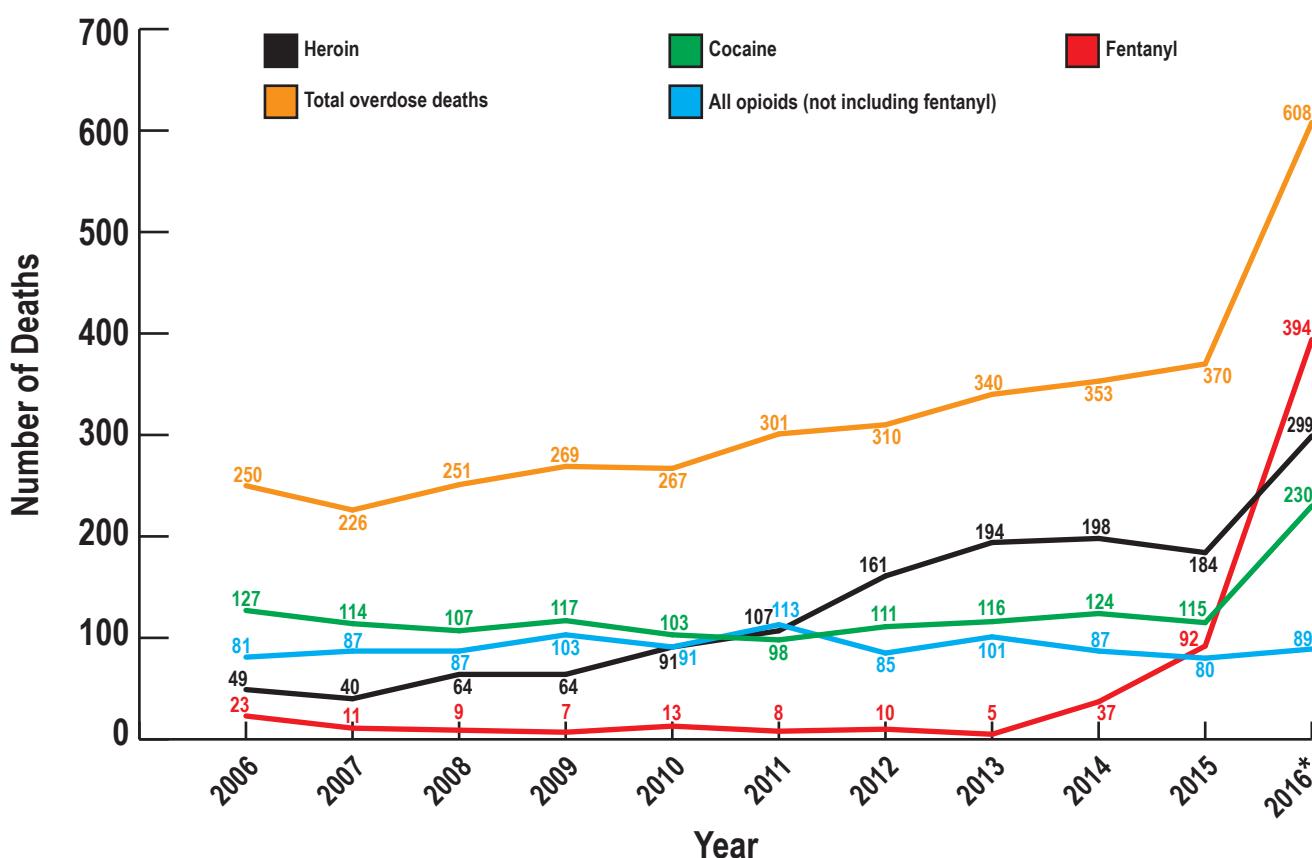


Figure 1: Cuyahoga County overdose deaths 2006-2016, most common associated drugs. 2016 cases projected from 3rd quarter data based on ruled cases as of December 31.

jected 59 up from 14). Deaths from cocaine alone are projected to rise from 42 to 61 (19 in total). Cocaine cases associated with fentanyl or fentanyl and other O/O taken in aggregate, are projected to rise from 24 to 123 (99 cases), representing 86% of the projected 100% increase of all cocaine-associated deaths in 2016. The impact of fentanyl on increased overall cocaine and heroin mortality is summarized in **Figure 2**. Rising heroin mortality in 2016 displays a similar pattern (**Figure 2**).

Table 1: Fentanyl Analogue Mortality, By Drug

| Analogues | Deaths through 2016 3rd Quarter |
|--------------------------------|---------------------------------|
| 3-Methylfentanyl | 4 |
| Acetylfentanyl | 32 |
| Carfentanyl or carfentanil | 23 |
| Despropionyl fentanyl (4-ANPP) | 3 |
| Furanylfentanyl | 6 |
| Other | |
| U-47700 | 2 |

Of note, drug submissions in the seized drug chemistry laboratory involving mixtures of illicit substances rose from 183 in the first nine months of 2015 to 733 in the same time period on 2016 (300%). Fentanyl was detected in only 35% of the 2015 mixtures compared to 61% of the 2016 mixtures.

Cuyahoga County's population, according to the U.S. Census Bureau 2015 estimate (8), is made up of 52.4% female and 47.6% male, 64.2% Caucasian, 30.3% African American, 5.6% Hispanic, 21.4% aged under 18, and 16.8% aged 65 and over (**Table 3**). In 2015, DRD occurred predominantly in males (71%), whites (75%) with an equal number of deaths in the 30-44 and 45-60 age groups (35% and 36%, respectively). Through the first three quarters of 2016, the patterns are males (72%) and whites (81%). Age distributions have been generally similar. These demographics are similar to our previous experience (5). Deaths associated with cocaine alone were the only group to show a non-white racial majority with 71% of these decedents being African-American. Deaths among fentanyl us-

Table 2: Drug Overdose Deaths (2015 and 2016), By Drug

| Drug(s) | Drug Deaths 2015 | Drug Deaths 2016 (3rd Quarter) |
|--|------------------|--------------------------------|
| Heroin alone | 84 | 43 |
| Drug-related deaths without Fentanyl, Heroin, Cocaine or Opioids | 47 | 20 |
| Cocaine alone | 42 | 46 |
| Opioids alone | 42 | 26 |
| Heroin + Cocaine | 37 | 23 |
| Fentanyl alone | 29 | 71 |
| Fentanyl + Heroin | 25 | 83 |
| Fentanyl + Heroin + Cocaine | 14 | 44 |
| Heroin + Opioids | 13 | 7 |
| Cocaine + Opioids | 10 | 9 |
| Fentanyl + Cocaine | 9 | 42 |
| Fentanyl + Heroin + Opioids | 8 | 8 |
| Fentanyl + Opioids | 6 | 11 |
| Heroin + Cocaine + Opioids | 3 | 2 |
| Fentanyl + Cocaine + Opioids | 1 | 4 |
| Fentanyl + Heroin + Cocaine + Opioids | 0 | 2 |
| Total | 370 | 441 |

ers (alone and mixed) showed a shift toward younger ages in 2016, with nearly 40% being between 30 and 44 years old and near equal percentages (24.6%) for ages less than 30 years and between 45 and 60 years (27.5%). Residency of decedents showed an approximately even divide between Cleveland and the remainder of Cuyahoga County, but factoring in DRD from out of county residents (primarily nonurban adjacent counties) produced a majority of suburban resident deaths (55% to 45%) that has remained consistent throughout the previous five years. By identified occupation, approximately 25% were manual

laborers (e.g., construction, repair, or production-type employment) but examination of occupations reported on death certificates revealed that approximately one-third were either unknown or too vague to permit classification. The highest attained educational level for the majority of DRD decedents was a high school diploma or less (70%).

The percentage of decedents with an OARRS report are listed in **Table 4**. Data shown for 2015 and 2016 are from the first four months of each year to permit an analysis of the efficacy of mandatory reporting.

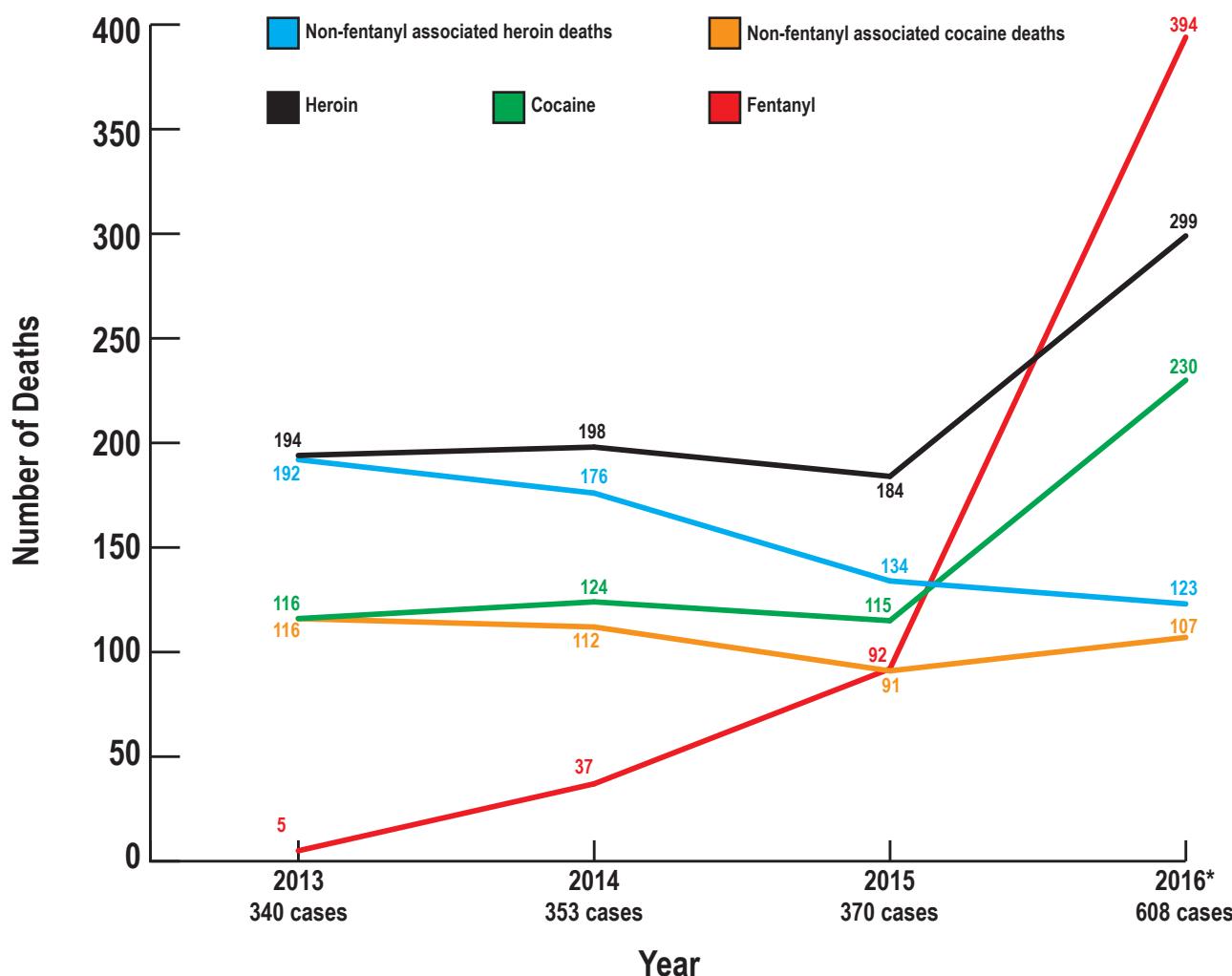


Figure 2: Cuyahoga County overdose deaths by year, drug and fentanyl contribution 2006-2016, most common associated drugs. 2016 cases projected from 3rd quarter data based on ruled cases as of December 31.

Table 3: General Population and Selected Drug Overdose Demographics (U.S. Census Data, 2015 Est. [8])

| | General Population Demographics | Percentage | Drug-Related Deaths Demographics | | Heroin-Related Deaths | | Fentanyl-Related Deaths | |
|-----------------------|---------------------------------|------------|----------------------------------|--------|-----------------------|--------|-------------------------|--------|
| Cuyahoga County Total | 1 255 921 | | 2015 | 2016 | 2015 | 2016 | 2015 | 2016 |
| City of Cleveland | 388 072 | 30.90% | 43.24% | 45.12% | 44.26% | 41.51% | 42.70% | 44.85% |
| Suburban Cuyahoga | 867 849 | 69.10% | 45.14% | 42.40% | 43.72% | 45.75% | 43.82% | 44.49% |
| Male | | 47.60% | 70.81% | 71.66% | 74.86% | 70.28% | 69.57% | 72.43% |
| Female | | 52.40% | 29.19% | 28.34% | 25.14% | 29.72% | 35.14% | 27.57% |
| White | | 64.20% | 74.86% | 80.73% | 83.06% | 89.62% | 74.16% | 87.87% |
| Black | | 30.30% | 24.59% | 18.59% | 15.85% | 9.91% | 25.84% | 12.13% |
| Asian | | 3.10% | 0.54% | 0.45% | 0.00% | 0.00% | 0.00% | 0.00% |
| Other | | 2.40% | 0.00% | 0.23% | 1.09% | 0.47% | 0.00% | 0.00% |
| Hispanic | | 5.60% | 3.51% | 2.72% | 5.46% | 3.30% | 3.37% | 2.94% |
| Age 18 under | | 21.40% | 0.54% | 0.91% | 1.09% | 1.42% | 1.12% | 1.10% |
| 19-29 | | 15.96% | 18.11% | 18.59% | 23.50% | 23.58% | 24.72% | 23.53% |
| 30-44 | | 17.97% | 35.14% | 32.65% | 40.44% | 33.49% | 38.20% | 39.34% |
| 45-59 | | 21.19% | 35.68% | 36.51% | 26.78% | 30.66% | 30.34% | 27.57% |
| 60+ | | 23.50% | 10.54% | 11.34% | 8.20% | 10.85% | 3.37% | 8.46% |

The OARRS trend is generally downward through 2015 (from a high of 73% in 2013 to 48% in following years) but improves back to earlier levels (71% in 2016) with the implementation of mandatory reporting. Of note, approximately one-third of the 2016 reports were of only three months duration or less prior to death.

DISCUSSION

The latest epidemic of drug-related deaths in the United States involves O/O and had its genesis in OPR (3, 4, 6). The problem evolved from OPR deaths to an explosive rise in illicit drug mortality, primarily heroin and in recent years, in clandestinely manufactured fentanyl. More immediately (especially the last six months of 2016), ever more potent analogues of fentanyl have been identified in Ohio (9) and in our jurisdiction specifically.

Our county data show a significant rise in heroin-associated mortality through 2013 with a leveling off in the following two years before a substantial rise in 2016. Fentanyl mortality has risen steadily since late 2014, with a sharp increase in 2016 (**Figure 1**). An earlier, minor spike in fentanyl mortality in 2006 was related to diversion of legal fentanyl, primarily in the form of transdermal patches. Opioid pain reliever deaths have not changed significantly in the last decade. This was also true of cocaine deaths until 2016, where they are

projected to double. The data further show that the increases in heroin and cocaine mortality are largely driven by lethal mixed intoxications where fentanyl is also present (**Figure 2/Table 2**). The substantial rise in drug mixtures (300% from 2015 to 2016) analyzed in the Crime Laboratory Seized Drug Chemistry Unit, with the most significant rise being in fentanyl mixtures, indicates that the upward trend in DRD involving these three leading drugs is most likely a reflection of increased fentanyl availability and mortality. The potency of fentanyl is approximately 10 to 20 times that of heroin, and cocaine is not a narcotic but abused for its stimulant properties. Our data indicate that the introduction of fentanyl into addict populations where mortality was stable (cocaine) or appeared to be stabilizing (heroin) has resulted in rises in cocaine and heroin mortality that are likely the manifestation of a skyrocketing fentanyl death rate rather than independent phenomena. Stated another way, heroin and cocaine mortality appear to be rising in our jurisdiction but it is likely that the abuse of these substances has not changed much; rather, the populations where they have been abused are now being exposed to more lethal mixtures of drugs (i.e., fentanyl) and mortality is trending upward because of the presence of this more lethal newcomer.

The recent appearance of fentanyl analogues in our jurisdiction (**Table 1**) and elsewhere has been associated with spikes in mortality (9). Many of these drugs (e.g., 3-methylfentanyl, carfentanil) have potencies well beyond fentanyl itself (anywhere from 4- to 120-fold for 3-methylfentanyl and 10- to 200-fold for carfentanil) and are a concern for even further worsening of the mortality trends. These drugs have also placed a burden on our laboratory both in detection and identification. With required limits of detection in the picogram per milliliter range for some of these compounds, it has been challenging to quantify them; lower concentrations also permit them to escape detection in routine screening tests. The identification of the analogues (and the procurement of appropriate standards) is another, often time-consuming, challenge for a laboratory already overburdened by the sheer volume of casework resulting from the overdose epidemic. It should be noted that if these analogues, especially the

Table 4: Drug-Related Deaths with a Prescription Drug Monitoring Program Report, By Year *†‡

| Year | Percentage of Decedents With Report |
|------|-------------------------------------|
| 2012 | 64 |
| 2013 | 73 |
| 2014 | 59 |
| 2015 | 48 |
| 2016 | 71 |

* Limited look back in 2012 (6-18 months), all other years: 24 months.

† Fentanyl data included since 2014

‡ 2015 and 2016 data include only first four months (see text)

more potent 3-methylfentanyl and carfentanyl, follow the same explosive growth trend of fentanyl as seen from November 2014 through 2016, we would fully expect fatality rates to continue rising due to the deadly potency of these newer synthetic opioids.

A look at the DRD victims reveals that gender, racial, and urban/suburban characteristics have remained similar. A trend toward younger ages has been noted with fentanyl, and a similar trend in all DRD has been detected but may again be driven by fentanyl's prominence in mixed drug intoxications. This shift may suggest the need for different strategies in public health interventions, particularly messaging to access the target audience.

Data from the OARRS registry are difficult to interpret because of changes in the program over the study period. Prior to mandatory reporting in OARRS, the general trend was downward with regard to the percentages of fatal illicit drug overdose victims who could be shown to have received a legal prescription for a controlled substance, most often OPR (**Table 4**). That raises an alarming possibility that addicts may be circumventing the previously well-established progression route from OPR to illicit drugs like heroin and fentanyl. Mandatory OARRS reporting saw a return to the higher percentages of illicit drug overdose victims with a history of legal OPR access, but the observation that a significant number of these addicts did not have a lengthy history (less than three months prior to death) in the legal health care system is troubling. While a PDMP cannot distinguish between the addicts who follow the route from OPR to heroin, and the addicts who use OPR and illicit drugs interchangeably, this trend raises concern that the current mitigation strategy of physician education in O/O prescribing practices and the use of PDMPs to identify at risk populations (10) may prove ineffective in reaching a significant subset of addicts. It will be essential to monitor this trend going forward as these mitigation strategies are viewed as cornerstones in the public health response. If this subset of illicit drug users largely bypasses the health care system in their descent into addiction, they will not benefit from either changes in prescribing practices or OPR surveillance.

It would be helpful to see if other jurisdictions, which did not see PDMP reporting fluctuations like we did over our study period, could confirm this downward trending and/or short duration of participation in the health care system. A population with minimal or no interaction with the health care system on the road to narcotic addiction will not benefit from OPR regulation or PDMP monitoring and will require different prevention strategies to be implemented.

Our data show a majority of fatal overdose victims achieve a final education level of a high school diploma or less. Occupational information indicates that at least one-quarter of the DRD decedents work or have worked in manual labor type occupations, which is all the more significant since a third of all decedents could not even be classified with regard to occupation based on death certificate information. The lack of advanced educational degrees may predict a higher level of manual laborers, who may in turn be more likely to suffer job-related injuries and subsequent treatment/overprescribing with OPR. These data support early educational efforts in schools and indicate that trade organizations and/or labor unions may be a productive partner in intervention efforts.

CONCLUSION

One clear lesson from the Cuyahoga County experience has been the critical role that the medical examiner's office can play in this epidemic. As an agency that is on the front lines of documenting the increase in DRD, our data are very close to real time and fill a gap in traditional public health approaches relying on aggregated death certificate data, which often lag behind by several to a few years. Our experience has shown that we are dealing with a crisis that has evolved rapidly in the emergence of fentanyl and now the fentanyl analogues. Thus, medical examiner data can potentially impact prevention efforts in a meaningful way because of the more timely nature of the information. We would also encourage health departments to engage their local death investigation agency (medical examiner or coroner) to access this "closer-to-real-time" information in addition to their larger aggregate data efforts. This information is also of con-



siderable value to law enforcement in their efforts as well. With the Crime Laboratory under the direction of the Medical Examiner in our jurisdiction, we have been fortunate to be able to facilitate frequent interactions between them and the Toxicology Laboratory (also under Medical Examiner direction), two critical players in any epidemic of DRD. Both laboratories have generated valuable information for the other and we would strongly encourage those jurisdictions where administrative control of these two laboratories is separate to explore options to encourage information sharing in a regular and timely manner. Funding and primary service responsibilities may limit the role such agencies can play in this effort (particularly in the time of an epidemic) but the quality and timeliness of their information should make the solution of these limitations a priority.

ACKNOWLEDGEMENT

The authors would like to thank Dr. Allison P. Hawkes for her contribution to data acquisition and analysis.

REFERENCES

- 1) Calcaterra S, Glanz J, Binswanger I. National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999-2009. *Drug Alcohol Depend.* 2013 Aug 1; 131(3):263-70. PMID: 23294765. PMCID: PMC3935414. <https://dx.doi.org/10.1016/j.drugalcdep.2012.11.018>.
- 2) Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers- United States, 1999-2008. *MMWR Morb Mortal Wkly Rep.* 2011 Nov 4; 60(43):1487-92. PMID: 22048730.
- 3) Warner M, Trinidad JP, Bastian BA, et al. Drugs most frequently involved in drug overdose deaths: United States, 2010-2014. *Natl Vital Stat Rep.* 2016 Dec; 65(10):1-15. PMID: 27996932.
- 4) Dasgupta N, Creppage K, Austin A, et al. Observed transition from opioid analgesic deaths to heroin. *Drug Alcohol Depend.* 2014 Dec 1; 145:238-41. PMID: 25456574. <https://dx.doi.org/10.1016/j.drugalcdep.2014.10.005>.
- 5) Gilson T, Herby C, Naso-Kaspar C. The Cuyahoga County heroin epidemic. *Acad Forensic Pathol.* 2014 Mar; 4(1):109-13. <https://doi.org/10.23907/2013.018>.
- 6) Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths: United States, 2000-2014. *MMWR Morb Mortal Wkly Rep.* 2016 Jan 1; 64(50-51):1378-82. PMID: 26720857. <https://dx.doi.org/10.15585/mmwr.mm6450a3>.
- 7) Gladden R, Martinez P, Seth P. Fentanyl law enforcement submissions and increases in synthetic opioid-involved overdose deaths - 27 states, 2013-2014. *MMWR Morb Mortal Wkly Rep.* 2016 Aug 26; 65(33): 837-43. PMID: 27560775. <https://dx.doi.org/10.15585/mmwr.mm6533a2>.
- 8) U.S. Census Bureau [Internet]. Washington: U.S. Census Bureau; c2017. American FactFinder: Annual estimates of the resident population for selected age groups by sex for the United States, States, Counties and Puerto Rico Commonwealth and Municipalios: April 1, 2010 to July 1, 2015; 2016 Jun [cited 2017 Jan 2]. Available from: <https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=bkmk>.
- 9) Healy J. Drug linked to Ohio overdoses can kill in doses smaller than a snowflake. *New York Times* [Internet]. 2016 Sep 5 [cited 2017 Jan 2]. Available from: <https://www.nytimes.com/2016/09/06/us/ohio-cincinnati-overdoses-carfentanil-heroin.html>.
- 10) Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain - United States, 2016. *JAMA.* 2016 Apr 19; 315(15):1624-45. PMID: 26977696. <https://dx.doi.org/10.1001/jama.2016.1464>.



Opioid Drug Death Investigations

Daniel Morgan

ABSTRACT

Opioid-related deaths have transitioned over the past 15 years, beginning with a steady increase in the incidence of fatal prescription overdoses, followed by a dramatic increase in deaths caused by illicit opioids, namely heroin and fentanyl. These trends in drug-related deaths are identified by medical examiners and coroners who serve an important role in public health surveillance. Medicolegal death investigators, being first responders, often recognize spates of drug-related deaths in real time. While few jurisdictions are unaffected by the epidemic, some medicolegal death investigators may have less experience detecting fatal opioid overdoses. This review will outline many of the medical, behavioral, and physical indicators of a deadly prescription or illicit opioid overdose. All aspects of a thorough medicolegal death investigation will be discussed, including the proper documentation of the scene and evidence handling. Investigative questions and follow-up procedures will also be reviewed. *Acad Forensic Pathol.* 2017;7(1): 50-59

AUTHORS

Daniel Morgan MS F-ABMDI, District of Columbia Office of the Chief Medical Examiner - Investigations

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

CORRESPONDENCE

Daniel Morgan MS F-ABMDI, 401 E St. SW, Washington DC 20024, daniel.morgan@dc.gov

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Medicolegal, Scene investigation, Opioids

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.006>

Submitted for consideration on 31 Dec 2016. Accepted for publication on 26 Jan 2017

INTRODUCTION

Beginning with a steady increase in the incidence of fatal prescription overdoses, there has been a dramatic increase in deaths caused by illicit opioids, namely heroin and fentanyl (1). These trends in drug-related deaths are identified by medical examiners and coroners who serve an important role in public health surveillance (2). In the early 2000s, medicolegal death investigators observed a spike in prescription drug overdoses with little foresight of the impending problem (3). As fatal overdoses consistently increased from year to year, medical examiners, coroners, and public health officials sounded the alarm of an epidemic. The law enforcement and regulatory response to the crisis was to crack down on pill mills, doctor shopping, and drug diversion. Addicts adjusted as well. Instead of swallowing prescription pills, abusers crushed and snorted them for a quicker sense of euphoria. Users also discovered methods to misuse fentanyl transdermal patches (4). As pills became more expensive and difficult to obtain, heroin filled the gap as a cheaper and more potent option. Beginning around 2010, the author began to see more syringes and drug paraphernalia at death scenes. The author also observed a shift in the demographics of the typical opioid abuser with the onset of the heroin epidemic. While adults over 40 made up the majority of prescription overdoses, more young adults between the ages of 20 and 40 began to die from heroin. Older adults also began to die from heroin. Illicitly manufactured fentanyl entered the scene soon after heroin (5). However, deaths from acute intoxication by all types of opioids continues to increase the caseloads of most medicolegal offices in the United States. Despite this increase, there are some regions of the country with limited experience investigating opioid fatalities. Medicolegal death investigators everywhere must be able to recognize potential opioid deaths to accurately determine jurisdiction. The need to thoroughly document the death scene and maintain proper chain of custody of evidence is critical as prosecutions of drug dealers for manslaughter are likely to increase (6).

DISCUSSION

Initial Report of Death

Medicolegal death investigators are tasked with detecting potential causes of death through direct observation of the death scene and by eliciting pertinent information from first responders during the initial report of a death. In some opioid overdoses, the cause of death seems immediately obvious to officials, requiring minimal exchange with the medicolegal death investigator during the first phone call. Other overdoses are more subtle and necessitate the investigator to inquire further when witnesses mention key words or medical conditions. Particular scene findings also require additional investigative effort to include or exclude intoxication as the probable cause of death. For instance, the complaint of “chronic back pain” prompts the investigator to explore the underlying disease or condition causing the pain. If the history includes back surgery, the decedent was probably prescribed an opioid at some point during treatment. Investigators should have a lower threshold for accepting cases in which controlled prescription drugs are present at the scene, especially if there are pill discrepancies noted. Another fine detail that introduces the possibility of an overdose often emerges during the witness’s recounting of the terminal circumstances. It is commonly reported that decedents were last known alive because they were snoring deeply and loudly, an indication of potential respiratory distress (7). A scene investigation should be conducted on every potential opioid overdose.

Scene Safety

Exercising scene safety is one of the primary tasks in every death investigation (8). In a drug-related case, the greatest threat or perceived threat to personal safety is a needle stick. Investigators and transport personnel are at highest risk for a needle stick while moving or manipulating the body. It is not uncommon for a syringe with a needle to be found underneath the body as the body is being turned over. Occasionally, the syringe is clutched in the decedent’s hand. Investigators must be hypervigilant when assessing the body

of a suspected intravenous drug abuser as a syringe is sometimes found in the decedent's pocket(s). A pat-down of the outer pockets will help identify a syringe. To avoid further risk of needle sticks, investigators should refrain from blindly reaching into trashcans or sweeping through the contents of open trash bags. Lastly, great care must be exercised at the time of needle collection.

Another danger to personal safety is inadvertent inhalation or absorption of illicit opioid powder. Illicit fentanyl can be so potent that minuscule amounts could cause death. While there are no reported cases of fatal exposure of law enforcement or forensics personnel in current literature, a number of medicolegal offices have purchased naloxone in the event of an accidental exposure (9). The frequency of these cases coupled with the potency of the drugs requires investigators to

use caution when evaluating the scene. Personal protective equipment is essential especially where multiple drug fatalities are suspected.

Scene Evaluation

After identifying the lead law enforcement officer, the investigator should request a guided tour of the scene. This "walk through" provides an opportunity for the officer to point out items he or she believes are significant and for the medicolegal death investigator to inquire about the integrity of those items. When initially viewing the decedent, his or her body position may reveal the first indication of an opioid overdose. In cases of acute intoxication, it is the author's experience that decedents are commonly found face down on their knees, suggesting sudden loss of consciousness (**Image 1**). When a body is discovered



Image 1: This man collapsed moments after injecting heroin into his arm. A wash cloth is clutched in his hand, which was likely used to wipe away blood from the injection site.

in this position, carefully inspect the immediate area for paraphernalia as a syringe or straw is likely underneath the body. Another immediately identifiable sign of an opioid overdose is the foam cone. This frothy buildup around the nose or mouth should be photographed at the time of the scene walk through as it is easily obliterated when the body is moved. While not pathognomonic of an overdose, overdose should be considered any time the decedent has a foam cone.

Investigating a Prescription Opioid Overdose

Prescription opioid overdoses are sometimes difficult to detect, most notably because there are legitimate medical conditions for which pain relief is needed. To further complicate the determination of jurisdiction, older adults may have a number of diseases that are equally as likely to have caused death as an overdose. As a result, the medicolegal death investigator must dig deeper into the decedent's medical, psychological, social, and behavioral histories to support or refute the investigative differential diagnosis of death by intoxication.

Several key words and findings also raise suspicions of prescription drug abuse. The most concerning is "pain management." Until recently, pain management patients were routinely prescribed a "cocktail" of medications including an opioid, benzodiazepine, and muscle relaxant. Whenever this combination of medications is present at the scene, jurisdiction should be considered. Prescription bottles with missing or obliterated labels can be a strong indication of misuse. Furthermore, possession of a prescription bottle belonging to someone else could be a sign of abuse. Another concerning finding is "doctor shopping" when the decedent has the same controlled substance from multiple prescribers (10). Doctor shopping may be detected by a prescription drug inventory at the scene or through a search of a state prescription drug monitoring program (PDMP).

A complete death scene investigation includes an inventory of prescription information and pill counts (11). In cooperation with law enforcement, the medicolegal death investigator should conduct a thorough

search of the residence for prescription bottles including medicine cabinets, kitchen cabinets, purses, refrigerators, nightstands, dresser drawers, and trashcans. Pill bottles, patches, and liquid (morphine) containers should be photographed so that all information on the front and back is legible. An overhead photo of the contents of the bottle(s) is also recommended. The following information should be recorded prior to securing the prescriptions in a bag: medication name, quantity prescribed, dosage directions, date filled, number remaining, and full name of the prescribing physician. If there is a pill discrepancy, the pathologist should be notified prior to the beginning of the autopsy.

Investigating an Illicit Opioid Death

Illicit opioid deaths are easily detected by investigators when the route of administration is intravenous injection; however, cases of powder insufflation (snorting) are more difficult to identify. In order to properly investigate these deaths, investigators must be familiar with the physical items associated with the preparation and administration of illicit opioids. Heroin and illicit fentanyl are generally encountered in powder form, though there have been recent reports of fentanyl pressed into tablets or filled in capsules (12). Heroin powder ranges in color from white to brown (**Image 2**) while illicit fentanyl is usually white. Intravenous drug abuse (IVDA) requires the user to carry or improvise a number of materials to prepare the illicit substance for injection. This IVDA kit is commonly referred to as "the works" (**Image 3**). The works includes a syringe with needle (used to aspirate and inject the illicit drug preparation), a "cooker" (a metal object, usually a spoon, bottle cap, or foil used to hold the powder and water mixture during heating), a heat source (lighter or candle used to heat the cooker in order to help dissolve the powder into the water), a filter (a small piece of cotton placed inside the cooker to capture solid debris as the liquid drug is drawn through the needle into the syringe), and a tourniquet (e.g., belt or shoelace used to increase the size of the vein for easier injection). Any time a metal spoon is found outside the kitchen, investigators should check the bottom of the spoon for soot and charring.



Image 2: Multiple resealable baggies containing heroin powder found in a decedent's pocket.

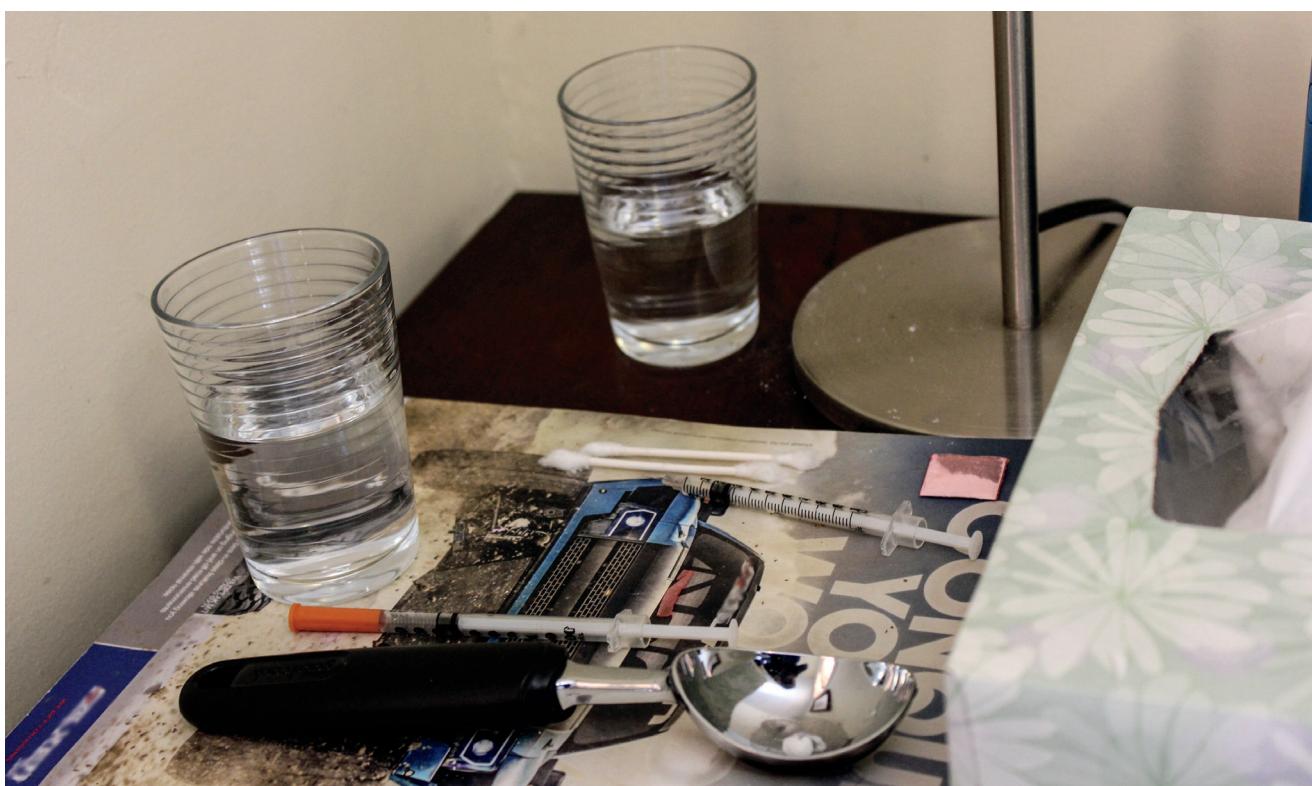


Image 3: Most of the supplies of a "works kit" including a cooker (ice cream scoop), syringe with needle, and filters (cotton swabs).

In addition to recognizing paraphernalia, it is important for investigators to document drug packaging as this information can be proactively communicated to the police or public during a spate of overdose deaths. Heroin packaging comes in various forms, but the most common are small plastic zip-top baggies, glassine envelopes, plastic bag corners ("tear offs"), cut/crimped plastic drinking straws, aluminum foil, and paper bindles (**Image 4**). The zip-top baggies and glassine envelopes are often stamped with an image or slogan. These images are useful to law enforcement tracking drug distribution networks.

Snorting opioid powder leaves behind little to no sign on the body. Most abusers will use a straw, so there may be no visible residue around the nares. That being said, there is paraphernalia associated with snorting drugs. Most commonly, cut straws, empty pen barrels,

or rolled bills are used and are frequently found in the decedent's pockets. If one of these items is found, investigators need to conduct a more thorough search of the scene for the remnants of drug packaging.

Documentation and Collection of Evidence

In a number of jurisdictions, the legal system has begun to approach overdose deaths with a focus on prosecution of drug dealers (5). Scenes are being managed more like homicides with a regard to evidence collection. This further underscores the importance of the scene briefing and walk through to discuss what items will be collected and by whom. If DNA collection is a consideration, then all persons entering the scene should consider increased personal protective equipment, including a facemask. Cell phones on the body have traditionally been treated as personal effects;



Image 4: Examples of common opioid powder packaging. Note that the plastic baggies are branded with an "eight ball" graphic.

however, cell phones contain critical information for the law enforcement investigation. If a phone is recovered from the pockets, it should be photographed and turned over to the police following proper chain of custody procedures.

After photographing prescription bottles, all controlled prescription drugs should be counted in the presence of a witness. The bottles are then placed in a tamper resistant evidence bag, marked with the case number, date collected, and signed or initialed by both parties. A chain of custody form should also be completed and accompany the bag of medications to the laboratory or other secure storage. In some jurisdictions, the medical examiner or coroner has legal authority to collect any item related to the cause and manner of death. In overdoses, this could include paraphernalia. If a syringe is to be collected, the investigator should place the needle and syringe in a sharps container, seal with evidence tape, and place the sharps container in a secondary container, usually a plastic evidence bag. Keep in mind that some crime laboratories will not accept a

syringe with a needle. In these cases, the investigator should contact the laboratory for proper evidence collection and submission techniques.

Evaluation and Documentation of the Body

Of course, a critical piece of evidence at any death scene is the body. There may be few external signs of an opioid overdose with the exception of intravenous injection cases. In these deaths, the investigator may observe acute venipuncture marks with or without contusion or blood around the injection site. The most common location for intravenous drug injection is the antecubital (AC) fossa. Veins in this location are easily accessible and easily hidden with clothing. After years of injections in the AC, chronic users may use alternate injection sites on the body. Other common locations are the groin and lower legs (**Image 5**). Investigators should use good judgment when searching the body for injection sites. If the body is in public view, it may not be advisable to pull down the decedent's pants to check for puncture marks in the



Image 5: Fresh needle injection of the lower leg. The decedent was unconscious before wiping away the blood.

groin. However, an investigator can easily remove a decedent's shoes and check between toes or slide their pant legs up to check the ankles and lower legs. Any time a decedent is wearing long sleeves and the cause of death is not clear, always slide the sleeves past the elbows to check for puncture marks.

Fentanyl transdermal patches are sometimes the source of the overdose. During examination of the body, investigators may encounter square or rectangular areas of adhesive residue on the skin. These patches are recommended to be placed on the upper arm, chest or back. Any time a decedent is found dead with a heating pad applied to the body, the investigator would be well served to check the area closely for a fentanyl patch. The application of heat to a fentanyl patch has been shown to increase the rapidity of absorption through the skin, which may result in injury or death (13).

Follow-up Investigation

Experienced investigators recognize that the scene examination is only the beginning of a comprehensive death investigation. In many fatal overdoses, there are no knowledgeable or reliable witnesses to confirm medical, psychological, and social histories. There-

fore, the medicolegal death investigator must contact family members and treating physicians after returning from the scene in order to determine whether or not the decedent abused illegal or prescriptions drugs. The following list of questions (**Figure 1**) will assist in obtaining a better understanding of the decedent's drug use history and potentially reveal additional sources of information (14).

When speaking with a treating physician, the investigator should specifically ask about known or suspected drug use. If the physician suspected drug use, what signs, symptoms, or behaviors did the decedent display during physical exam or history? Did the physician ever order a drug screen?

Medicolegal death investigators should also have access to prescription drug monitoring programs in their jurisdiction. These databases are useful in identifying patients who attempt to obtain the same narcotic prescriptions from different physicians without the physicians' knowledge of the other prescriptions. Prescription drug monitoring program databases may be helpful in cases where the cause of death is not clear after completion of the scene investigation. A search of the PDMP should be a standard procedure in most accepted and declined cases.

Has the decedent ever used illegal drugs or abused prescriptions?

- If yes, what kind? How often? When was the last use? How long has he or she been using?
- How do they use (route of administration)?
- Has he or she ever been hospitalized for an overdose? When? Where?
- Has he or she ever been in drug rehabilitation?

What precipitated initial use (it may be related to an injury)?

How long has the decedent been sober?

- Any recent life events that may have triggered relapse?
- Has the decedent been recently incarcerated or otherwise unable to use drugs?

Any indication this was an intentional overdose?

Who is the primary care physician? Are there any other treating physicians?

Figure 1: List of questions to assist in obtaining a better understanding of the decedent's drug use history.



An emergency medical services (EMS) incident report (“run sheet”) should be requested in all these cases as some acute venipunctures could be the result of resuscitative efforts rather than intravenous drug abuse. If the EMS record does not adequately document the treatment, then an interview may be necessary.

CONCLUSION

From the initial phone call through the completion of post-scene interviews, medicolegal death investigators need to be alert for explicit as well as subtle indications of a deadly overdose. The reporting party might mention details such as “heavy snoring” or “pain management” triggering the investigator to ask further questions and more than likely warranting a scene response. In the author’s experience, the position of the body may also yield the first clue of a fatal overdose. Even a history of opioid abuse unaccompanied by other supporting facts or findings could be sufficient to accept jurisdiction on a case. Once jurisdiction is accepted, a scene investigation should be conducted on all opioid drug deaths.

At the scene, investigators must document physical findings of an opioid drug death while exercising extreme caution when manipulating the body. Findings in a prescription drug death include multiple bottles of the same opioid from different prescribers, discrepancies in pill counts, or a heating pad applied to a transdermal patch. A pill inventory should be a standard practice in all suspected prescription drug overdoses. Common illicit opioid paraphernalia including cut straws, empty pen barrels, and “works kits” need to be photographed and collected in accordance with local laws and practices. After the scene has been documented, the investigator should examine the body with great care as syringes with needles are frequently discovered immediately underneath the body, in the pockets of clothing, or clutched in a decedent’s hand. Illicit fentanyl and fentanyl analogs present a serious threat to the health of investigators as minute amounts of the powder could be inhaled or absorbed. Personal protective equipment, including a properly fitted face mask and gloves, should be worn to reduce the risk of exposure and to protect against unintentional contam-

ination of the drug packaging with an investigator’s own DNA.

The medical examiner or coroner is uniquely positioned to deliver useful data to policy makers and law enforcement officials to inform prevention and response strategies. By conducting a thorough follow up investigation on every opioid drug death, the medical examiner or coroner’s office is able to provide the public health community with potential points of intervention to help reduce future deaths. Furthermore, scene photographs of drug packaging can be shared with local and regional law enforcement to aid in the identification of drug distribution networks. The medicolegal death investigator’s documentation of an opioid drug death not only assists in the determination of cause and manner of death, but also provides valuable information to support public health and safety initiatives.

REFERENCES

- 1) Rudd R, Seth P, David F, Scholl L. Increases in drug and opioid-involved overdose death—United States, 2010–2015. *MMWR Morb Mortal Wkly Rep.* 2016 Dec 30; 65(5051):1445–52. PMID: 28033313. <https://doi.org/10.15585/mmwr.mm655051e1>.
- 2) Hanzlick R. Medical examiners, coroners, and public health: a review and update. *Arch Path & Lab Med.* 2006 Sep; 130(9): 1274–82. PMID: 16948511.
- 3) Dart R, Surratt H, Cicero T, et al. Trends in opioid analgesic abuse and mortality in the United States. *N Engl J Med.* 2015 Jan 15; 372(3):241–8. PMID: 25587948. <https://doi.org/10.1056/nejmsa1406143>.
- 4) Jumbelic M. Deaths with transdermal fentanyl patches. *Am J Forensic Med Pathol.* 2010 Mar; 31(1):18–21. PMID: 19918162. <https://doi.org/10.1097/paf.0b013e31818738b8>.
- 5) Gladden R, Martinez P, Seth P. Fentanyl law enforcement submissions and increases in synthetic Opioid-involved overdose deaths—27 states, 2013–2014. *MMWR Morb Mortal Wkly Rep.* 2016 Aug 26; (65):837–843. PMID: 27560775. <https://doi.org/10.15585/mmwr.mm6533a2>.
- 6) Harvey KB. Responding to the heroin crisis: two initiatives in the Eastern District of Kentucky. *US Attorneys' Bull.* 2016 Sept; 64(5):37–43.
- 7) Oliver P, Rouse G, Kean J, Forrest R. Snoring prior to overdose: an intervention opportunity. *Addiction.* 2001 Apr; 96(4):652. PMID: 11345948.
- 8) Death investigation: a guide for the scene investigator [Internet]. Washington: National Institute of Justice; 2011 Jun [cited 2016 Dec 31]. 64 p. Available from: <https://www.ncjrs.gov/pdffiles1/nij/234457.pdf>.
- 9) Miller N. With rise of carfentanil, ME office is carrying Narcan to protect staff. Orlando Journal Sentinel [Internet]. 2016 Nov 23 [cited 2016 Dec 20]; Health. Available from: <http://www.orlandosentinel.com/health/addiction-recovery/os-medical-examiner-carries-narcan-for-carfentanil-20161123-story.html>.



- 10) Public health law: doctor shopping laws [Internet]. Atlanta: Centers for Disease Control and Prevention; [cited 2016 Dec 31]. 8 p. Available from: <https://www.cdc.gov/phlp/docs/menu-shoppinglaws.pdf>.
- 11) Davis GG; National Association of Medical Examiners and American College of Medical Toxicology Expert Panel on Evaluating and Reporting Opioid Deaths. National Association of Medical Examiners position paper: recommendations for the investigation, diagnosis, and certification of deaths related to opioid drugs. *Acad Forensic Pathol.* 2013 Mar; 3(1):77–83. <https://doi.org/10.23907/2013.011>.
- 12) Kamp J, Campo-Flores A. The pill makers next door: how America's opioid crisis is spreading. *Wall Street Journal* [Internet]. 2016 Oct 5 [cited 2016 Dec 31]; General news. Available from: <http://www.wsj.com/articles/the-pill-makers-next-door-how-americas-opioid-crisis-is-spreading-1475693346>.
- 13) U.S. Food and Drug Administration [Internet]. Washington: U.S. Food and Drug Administration; c2016. FDA issues second safety warning on fentanyl skin patch; 2007 Dec12 [cited 2016 Dec 31]. Available from: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109046.htm>.
- 14) Cuyahoga County Medical Examiner's Office medicolegal death investigation field guide. Cleveland: Cuyahoga County Department of Public Works: Printing and Reproduction Services; 2015. 131 p.



Drug Overdose Surveillance and Information Sharing Via a Public Database: The Role of the Medical Examiner/Coroner

Karl E. Williams, Michael D. Freeman, Lynn Mirigian

ABSTRACT

The medical examiner/coroner (ME/C) death scene investigation systems of the United States play a pivotal role in the current public health crisis created by the expanding drug dependency epidemic in the United States. The first point of recognition of a drug-related death in a community is often the local ME/C agency. This circumstance places these entities in an ideal position to provide surveillance data regarding the epidemiology of drug-related deaths occurring within the jurisdiction of the agency. The ability to surveil for the distribution and determinants among drug-related deaths at the first point of contact enhances the capacity to recognize actionable trends at the local, state, and national levels, including the ability to identify secular (longer-term) trends among various drugs and population subgroups, as well as activity spikes (outbreaks) associated with high-potency formulations and drug combinations.

In this article, we describe the development and implementation of an online website that provides public access to a wide array of drug-related death surveillance resources and tools. The website gives users access to a detailed dataset that includes information regarding specific drugs, demographic information pertaining to the decedent, and to investigational findings related to the circumstances of the death. A unique aspect of the database is that it is populated by ME/C agencies and accessed by the public with no intermediary agency, so that the lag time between the identification and investigation of the death as drug-related and community knowledge of the circumstances of the death is minimized.

Wide dissemination of accurate drug death surveillance information in an easily accessible and customizable format promotes societal awareness of the drug death epidemic, but also provides information to public health, law enforcement, regulatory, and other community-based organizations that can benefit from the most up-to-date knowledge. We envision a national system of surveillance at the regional ME/C level that would allow for optimal information dissemination and sharing. Such a system would likely allow for more efficacious allocation of resources at the regional and national level. *Acad Forensic Pathol.* 2017 7(1): 60-72

AUTHORS

Karl E. Williams MD MPH, Allegheny County Office of the Medical Examiner and University of Pittsburgh, School of Pharmacy

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, principal investigator of a related study listed in the citations, general supervision, general administrative support, writing assistance and/or technical editing.

Lynn Mirigian PhD, Program Evaluation and Research Unit, University of Pittsburgh, School of Pharmacy

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, general supervision, writing assistance and/or technical editing.

Michael D. Freeman MedDr PhD MPH, Oregon Health & Science University School of Medicine - Department of Psychiatry

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, writing assistance and/or technical editing.

CORRESPONDENCE

Karl E. Williams MD, 1520 Penn Ave, Pittsburgh PA 15219, karl.williams@alleghenycounty.us

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript



DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

This work was presented at the 2016 NAME Annual Meeting. The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Drug overdose, Surveillance, Public access, Searchable

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.007>

Submitted for consideration on 6 Jan 2017. Accepted for publication on 4 Feb 2017

INTRODUCTION

Over the ten-year period from 2005 to 2014, drug overdose deaths in the United States increased at an alarming rate. Deaths due to illicit drug overdoses doubled during this time (from 8923 to 17 465), a rise driven almost entirely by a 5.3-fold increase in heroin-related deaths (from 2009 to 10 574) (1). Prescription drug deaths also increased during this same time, though at a lower rate (1.7-fold, from 15 352 to 25 760), with the largest numbers of deaths resulting from opioid overdoses, which increased 1.7 times, from 10 928 to 18 893 (1). In 2015, there were more than 33 000 deaths attributable to either opioid prescription drugs or heroin, causing the Centers for Disease Control and Prevention to characterize the deaths as part of a nationwide epidemic (2).

The recognition of a death as drug-related is typically first made by the medical examiner or coroner's office, and the majority of such deaths are investigated via autopsy. Of the 55 403 deaths in 2015 deemed drug-related, 40 411 (73%) underwent autopsy examination (3).

Medical examiner/coroner (ME/C) agencies are ideally situated to provide comprehensive and contemporaneous information regarding drug-related deaths, such that they can function as epidemiologic surveillance sites. Surveillance is a critically important response to the nationwide drug death epidemic, given the high degree of secular variation in geographic distribution, victim demography, drug types and combinations, and other factors. Timely dissemination of surveillance data allows for rapid identification of outbreak-type spikes in deaths resulting from the introduction of particularly lethal street drugs. In an ideal system, ME/C agencies can make death investigation information that is routinely gathered for drug overdose deaths directly available to all local, statewide, and national stakeholders in an easily searchable format. Such a system would enhance strategies for prevention and deterrence, allowing for a more efficient allocation of resources.

In the following discussion, we present the background, methodology, and plan for a ME/C-based

drug overdose surveillance system that is being successfully implemented in the Commonwealth of Pennsylvania.

DISCUSSION

Drug Overdose Death Investigation in Pennsylvania

Pennsylvania has a population of approximately 13 million people, with 67 county jurisdictions divided into eight classes. Investigation of deaths that occur in the Commonwealth of Pennsylvania come under the jurisdiction of either a ME (two) or an elected lay-coroner (65). The two largest counties, Philadelphia (Class 1), with a population of 1.5 million, and Allegheny (Class 2), with a population of 1.2 million, have appointed medical examiner death scene investigation systems. The remaining Class 3 through Class 8 counties, ranging in population from 5000 to 800 000, have elected lay-coroners. The majority of these elected coroners are funeral directors.

Provision of autopsy services is by salaried, board-certified forensic pathologists in the two ME systems, and by a mixture of individual and group forensic practices, also staffed in virtually all instances by forensic pathologists, in the remaining jurisdictions. Throughout the state, these local agencies suffer from historic and chronic underfunding, now accentuated by the continually increasing demand from the overdose epidemic. Death investigation practices and customs are nonstandardized in the Commonwealth, and there is no statewide mandate, as in some jurisdictions, to include specific drugs on the death certificate. This is one of the reasons that Pennsylvania ranks within the bottom five percent of accuracy of death certification with the United States (4).

Although there is significant variation in practice, the investigation of the vast majority of apparent drug overdoses in Pennsylvania generally includes performance of a complete autopsy, including testing of urine and at least one source of blood. Most, but not all, jurisdictions follow the investigation protocol recommended by the National Association of Medical Examiners, which includes review of the death



scene and available documentation of history of drug abuse, identification of drugs found at the scene, and prescription drug history (5).

Each of the two ME systems in the Commonwealth have independent toxicology sections. Toxicology for the majority of the elected Pennsylvania Coroners is most commonly performed by National Medical Services of Willow Grove, Pennsylvania. In both instances, testing is performed on specimens of blood and/or urine and includes all major drugs of abuse. As would be expected, and as between any jurisdictions outside PA, variation between the specific specimens submitted, methodology employed, composition of test panels, and ability to perform expanded and focused testing creates an additional element of nonstandardization.

The Allegheny County Office of the Medical Examiner (ACOME) is unusual in that it has independent toxicology and drug chemistry sections located within the same facility as where autopsies are performed. This arrangement allows for expanded and/or focused testing on drugs seized from the death scene, as necessary, as well as readily available consultation with scene investigators and pathologists. Drug seizures from the scenes of overdose deaths in counties represented by coroners are typically submitted to the crime laboratories of the Pennsylvania State Police (PSP), a statewide system of six regional labs.

OverDoseFreePA

In 2010, the Allegheny County Overdose Prevention Coalition (ACOPC) was established to address the expanding overdose crisis in Allegheny County (6). The Coalition is hosted by the School of Pharmacy of the University of Pittsburgh, and consists of a broad-based alliance of community, law enforcement, governmental, and pharmaceutical entities, along with academic stakeholders. In 2013, the coalition was expanded to establish OverDoseFreePA (OFPA), a group focused more directly on overdose deaths in Pennsylvania (7).

The primary aims of ACOPC are twofold. The first is to provide a comprehensive source of advice on approaches to the overdose crisis through its web-based

catalogue of resource and a Technical Advisory Center (TAC) (8). To this end, the TAC has established strategic alliances with 14 counties.

The second goal is to establish and publish through OFPA a standardized, publicly available dataset of drug overdose deaths in the Commonwealth. Currently, an overlapping subset of 11 counties in the Commonwealth actively contributes their overdose data to OFPA. The site is designed to enable data entry by either ME/C personnel, such that the results could be incorporated into this publicly available, web-based interface in a timely manner. For jurisdictions with more advanced information systems, submission to the site can be handled as a bulk upload.

Overdose Death Registry Data Entry Protocol

Participating ME/C agencies submit information into an online form that includes all available demographic and scene investigation findings in addition to the information from the toxicology reports (**Figure 1**). Medical examiner/coroner staff tasked with submitting data to OFPA receive training from OFPA personnel in basic toxicology and use of the drug entry form. Additionally, OFPA provides online support and a dictionary of drugs and metabolites via the TAC. Turnaround time from the date of death to toxicology results is typically two to three weeks in the ME/C agencies throughout the Commonwealth, and once the results are received they are submitted to OFPA within one to four weeks. Thus, the lag time between an overdose death and online publication is typically no more than two months for any death.

Participation in OFPA is uncompensated at the present time. The motivation to contribute data is primarily attributable to a sense of community service and the widely recognized need in the ME/C system for accurate and timely data regarding overdose deaths.

The drug data portion of the entry form permits categorization of each agent as either a parent drug or metabolite, with only the parent drug listed as contributing to the death. There is an additional capability to enter specific measured concentrations of the identi-

fied agents. The online drug dictionary includes any drug or metabolite that has appeared in a submitted case from any jurisdiction and allows ME/C personnel to have specific information as to the nature of each agent identified in their particular toxicology report. This capability assists contributors in determining whether the specific agent is a parent drug and main cause of death, a contributory agent, or a metabolite. It also aids in understanding metabolic pathways. Com-

monly found agents such as cannabinoids, nicotine, and therapeutic levels of nonscheduled drugs are not included as a contributor but are retained in the ultimate dataset for possible future consideration.

Following completion of the entry form, the individual case is placed into the “Review Case Data” queue for vetting by the technical staff of OFPA for accuracy and consistency (**Figure 2**). Staff consists of personnel

The screenshot shows a web-based application interface for managing overdose cases. On the left, there's a sidebar with links for Home, News, Overdose Data, Education, Local Resources, About, TAC, and Emergency? (which is highlighted in red). The main content area has two main sections: "Case Data" and "Drugs".

Case Data: This section contains several input fields with blacked-out values. The fields include: county, me_case, manner, coded_cause, case_year, state_file, autopsy, death_date, death_time, and incident_zip.

Drugs: This section displays a table of substances found in the case. The columns are: ID, Name, Source, Level, Unit, Type, Parent, and Contributor.

| ID | Name | Source | Level | Unit | Type | Parent | Contributor |
|----|-----------------|---------|-------|--------|------------|-------------------------------------|-------------------------------------|
| 2 | Benzoylecgonine | heart t | 210 | ng/mL | Drug | | <input checked="" type="checkbox"/> |
| 3 | Fentanyl | heart t | 0.22 | ng/mL | Drug | | <input checked="" type="checkbox"/> |
| | Norfentanyl | heart t | 1.2 | ng/mL | Metabolite | 3 | <input type="checkbox"/> |
| 1 | Lorazepam | heart t | 11 | ng/mL | Drug | | <input checked="" type="checkbox"/> |
| | | Select | | Select | Drug | <input checked="" type="checkbox"/> | Add Drug |

At the bottom of the Drugs section, there are buttons for "Delete" and "Add Drug". Below the Drugs section, there is a "Comment/Notes" field.

Figure 1: Screenshot of portion of data entry form.

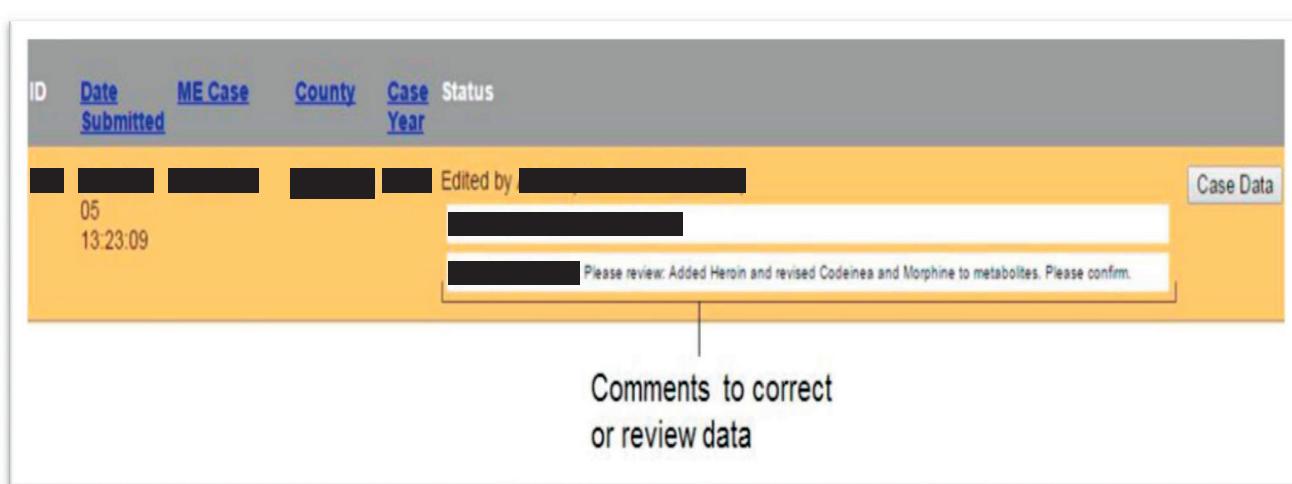


Figure 2: Screenshot of online communication with contributor during case review.

with at least master's level training in pharmacology or toxicology. The review process initiates a two-way, online conversation with the submitting jurisdiction concerning details of the particular case (**Figure 3**). The process for filing the majority reports is relatively straightforward.

At this stage of the process, consultation on more complex issues, such as postmortem redistribution and metabolism, can be provided by OFPA personnel with specific training and with backup assistance from consulting forensic toxicologists and medical examiners.

While in most cases the offending drug is readily identified, in some cases, the relative contribution of several drugs needs to be assessed. The general rule followed in multidrug cases is that it is not typically feasible to quantify the role that an individual drug played in causing a death. Thus, the procedure in OFPA is to be inclusive and consider all drugs identified at more than trace amounts as contributing to the death (9). This practice sidesteps the wide variety of interpretive and technical issues that can arise when analyzing the results of a toxicological analysis. Some of these issues present difficulties even for the larger

ME jurisdictions with in-house toxicologists. Despite these potential difficulties, the vast majority of cases are using a rational "best effort" approach.

The most common problems with interpreting toxicology reports occur with opioid drugs and benzodiazepines. For opioids, the problem results from finding morphine in the urine without the presence of either heroin or 6-monoacetylmorphine (6-MAM) in any other tested fluids. The presence of one or the other would indicate that the parent drug was heroin, but when neither is found, the cause of the overdose is less certain. While this issue has been addressed in the literature with sophisticated algorithms (10, 11), the approach used when the paradox is encountered for OFPA data is to consider the presence of morphine as representing the "last man standing" of a heroin overdose. When considered along with secondary factors such as evidence of active drug use from the scene, history of drug abuse, injection sites on the body, and urine drug screens, this probabilistic approach is most practicable (12).

The second class of drugs that can present issues in interpretation of toxicology reports is benzodiazepines.

The screenshot shows a software application window titled "Case Data". On the left, there is a sidebar labeled "Edit case data" containing various input fields for case information like county, me_case, manner, coded_cause, case_year, state_file, autopsy, death_date, death_time, incident_no, death_count, incident_memo, death_place, and death_place_annotation. Above these fields is a timestamp: 106 2015-08-2012-149 Armstrong 2012 Edited by Admin (2015-11-02 15:52:42). Below the sidebar is a "Drugs" section with a table:

| ID | Name | Source | Level | Unit | Type | Parent | Contributor | Action |
|----|------------|--------|--------|--------|------------|--------|-------------------------------------|----------|
| 4 | Alprazolam | blood | Select | Select | Drug | | <input checked="" type="checkbox"/> | Delete |
| 5 | Heroin | Select | Select | Select | Drug | | <input checked="" type="checkbox"/> | Delete |
| | Codine | blood | Select | Select | Metabolite | 5 | <input checked="" type="checkbox"/> | Delete |
| | Morphine | blood | Select | Select | Metabolite | 5 | <input checked="" type="checkbox"/> | Delete |
| 3 | Oxycodone | blood | Select | Select | Drug | | <input checked="" type="checkbox"/> | Delete |
| | | Select | Select | Select | Drug | | <input checked="" type="checkbox"/> | Add Drug |

Below the table is a "Comment/Notes" section with a large text area and an "Update Case" button at the bottom.

Annotations on the right side of the interface point to specific features:

- A pointer labeled "Edit drug data" points to the "Edit drug data" column in the table.
- A pointer labeled "Leave a comment fo the administrator" points to the "Comment/Notes" text area.

Figure 3: Screenshot demonstrating editing and revision of original drug data.

These drugs share common structures and are extensively metabolized, often to clinically active agents that can be utilized for their therapeutic effect. This can result in difficulties determining the drug of origin. OverDoseFreePA provides guidance in the resolution of problem cases.

For remaining drug classes (central nervous system stimulants/selective serotonin release inhibitors) and individual agents, such as fentanyl and its analogues, ethanol, and prescription opioids, the determination of contribution to the overdose is typically made without difficulty.

Data Synthesis and Publication

Following approval of the individual case by the submitting jurisdiction, the data are moved to the “Live Data” section of the site and made available for public access. The view presented on entry into the OFPA site is static, and includes the following: total overdoses by region (by specific county or aggregate of one or more contiguous jurisdictions, and for variable number of specified years dating back to 2007), gender, race, age, place of injury ZIP code, top ten drugs detected, and top ten fatal drugs over time (**Figures 4, 5, and 6**).

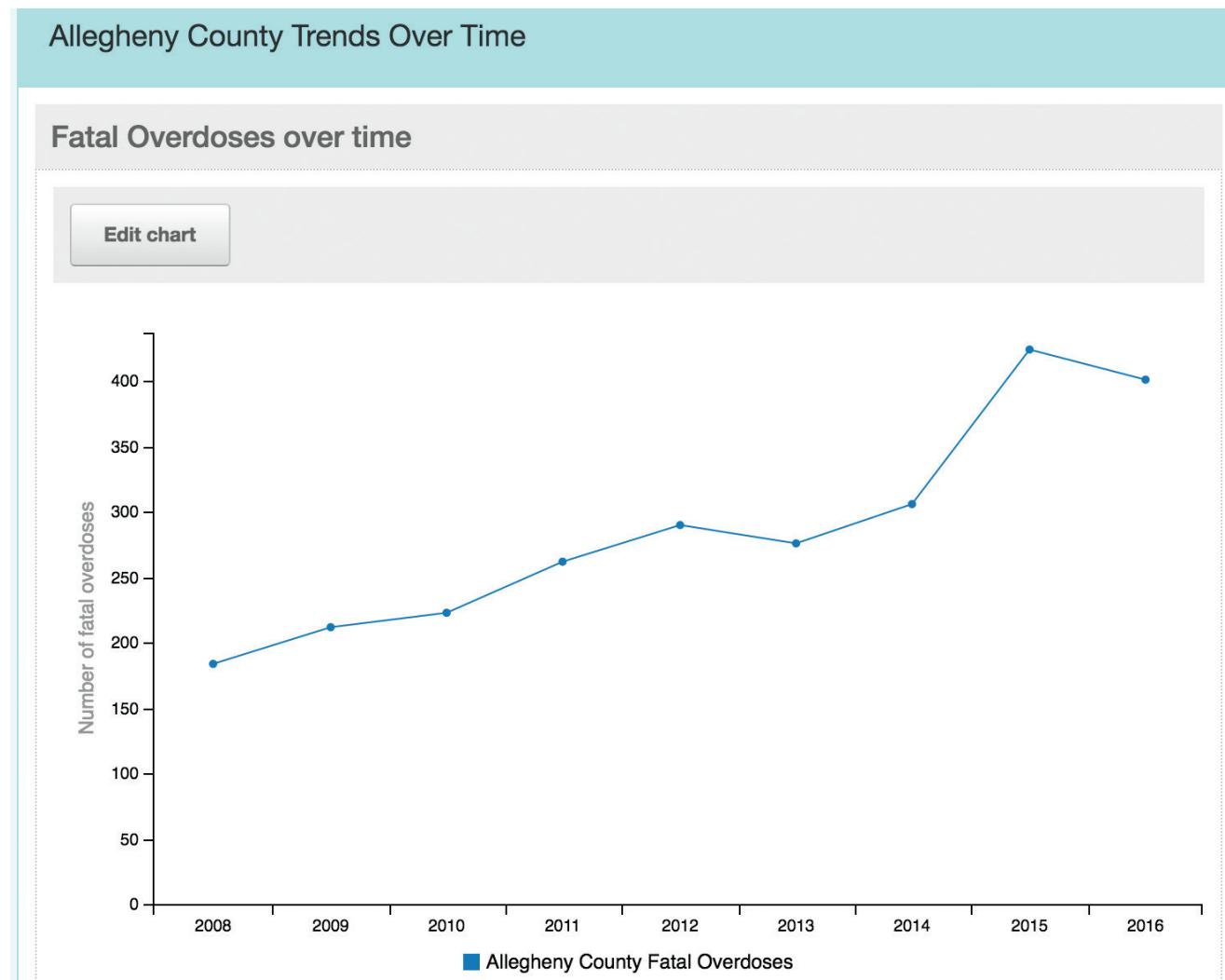


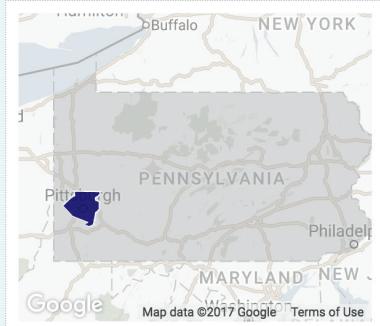
Figure 4: Screenshot showing fatal overdoses in Allegheny County over time.

Select a region or county:

Allegheny County

Allegheny County

A



Allegheny County data is updated on a monthly basis. This database reflects complete records from 2011-2015. 2016 is in progress. The data sets for years 2008-2010 are incomplete as the Medical Examiner's office continues to review and upload records from this time period.

Approximately 50% of the records from 2008-2010 have not been cleared.

If you have questions about Allegheny County's data, please contact:

Dr. Karl Williams MD, MPH, Medical Examiner, 1520 Penn Avenue Pittsburgh, PA 15222, Phone: (412) 350-4800, Fax: (412) 350-4899

2,578

reported overdose deaths in All Years Available (2008 - 2016)

Allegheny County Demographics of Overdose Decedents (All Years Available (2008 - 2016))

B

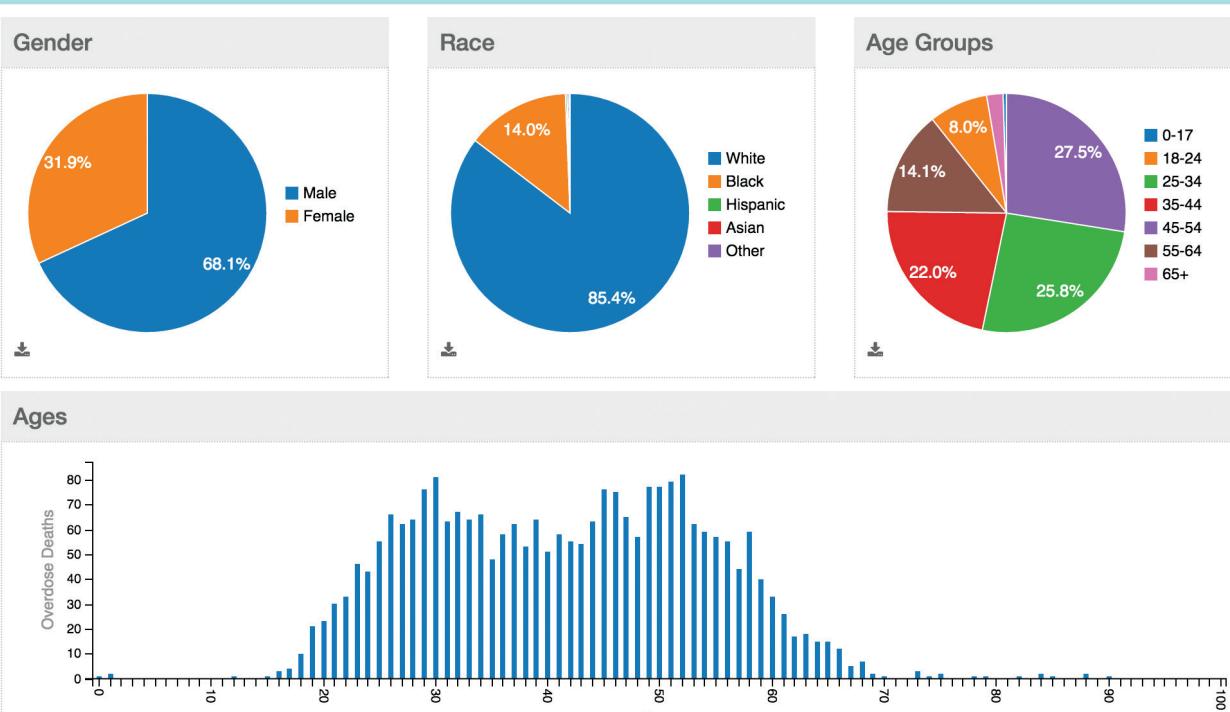


Figure 5: A) Screenshot showing reported overdose deaths in Allegheny County over all years in the database. B) Screenshot showing demographics of fatal overdose decedents.

The OFPA site allows for the ability to create customized queries of the entire dataset using the above-listed set of variables.

Data and Examples

OverDoseFreePA currently includes participation, at some level, by 46 of the 67 counties of the Commonwealth, including two overlapping subsets of counties.

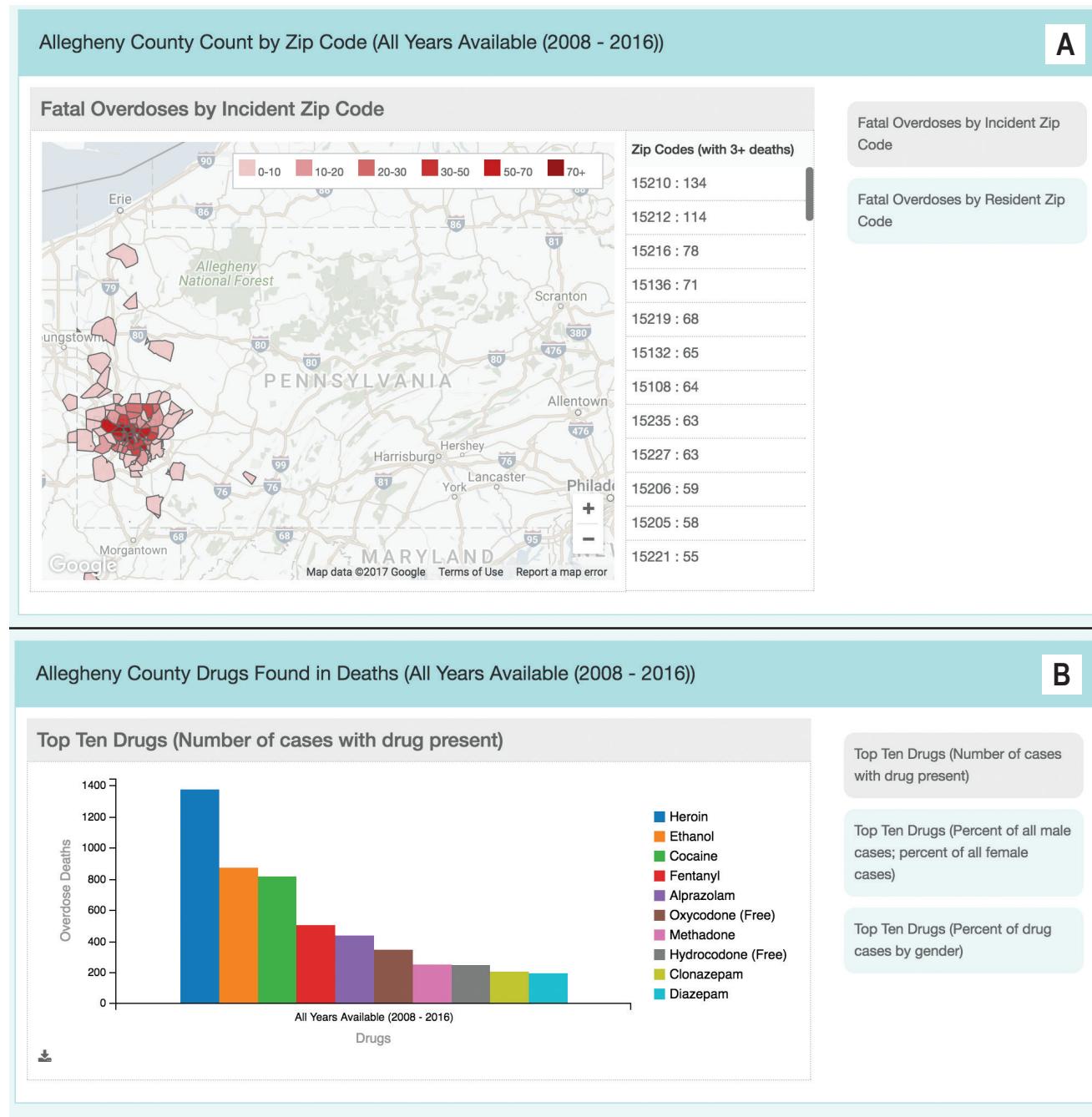


Figure 6: A) Screenshot showing fatal overdoses by zip code. B) Screenshot showing the top ten drugs involved in overdose deaths.

There are ME/C agencies in 11 counties that are currently submitting overdose data as of December 2016, and an additional 26 counties with an alliance with the University of Pittsburgh School of Pharmacy Technical Assistance Center. The total group represents approximately half of the population of the Commonwealth. Data from more than 4000 overdose deaths are currently available on the OFPA website, and for two of the counties complete data on the site dates back to 2007.

A prominent feature of the OFPA website is the contemporaneous availability of raw data concerning drug overdose deaths to the public, as well as the ability for any site user to formulate unique queries of the data. Anonymized overdose information is considered to be in the public domain. With the OFPA website, this information is made immediately available to all stakeholders, including law enforcement at local, state, and national levels, local public health groups, media, and concerned individuals.

The following examples demonstrate a small sample of the flexibility and utility of the website:

- 1) Allegheny County's fentanyl experience, 2007-2016 (**Figure 7**). Prior to the obvious inflection point occurring in 2014, the experience in the county was primarily with diverted pharmaceutical fentanyl in the form of Duragesic patches. In January 2014, Allegheny County experienced a brief epidemic consisting of 27 heroin/fentanyl deaths occurring over a three-week period (13). The deaths marked the beginning of a steady rise in fentanyl-related deaths that has been observed nationwide. As can be seen in the incomplete data for 2016 in **Figure 7** (11 months of data), the increase in fentanyl-related overdose deaths has persisted.
- 2) Heroin experience in Westmoreland County by sex, age group, and race, 2009-2016 (**Figure 8**).

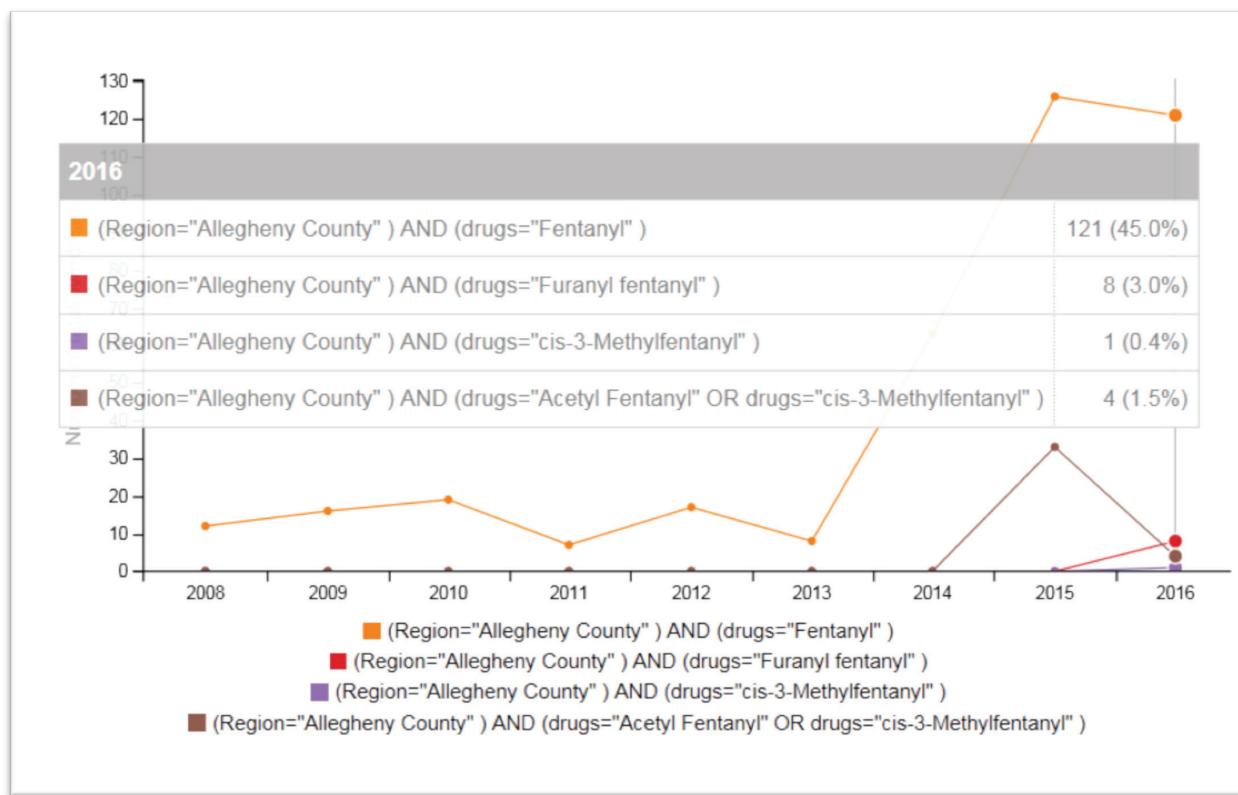


Figure 7: Screenshot generated by a query on Allegheny County's experience with fentanyl and fentanyl analogues (2007 – 2016).

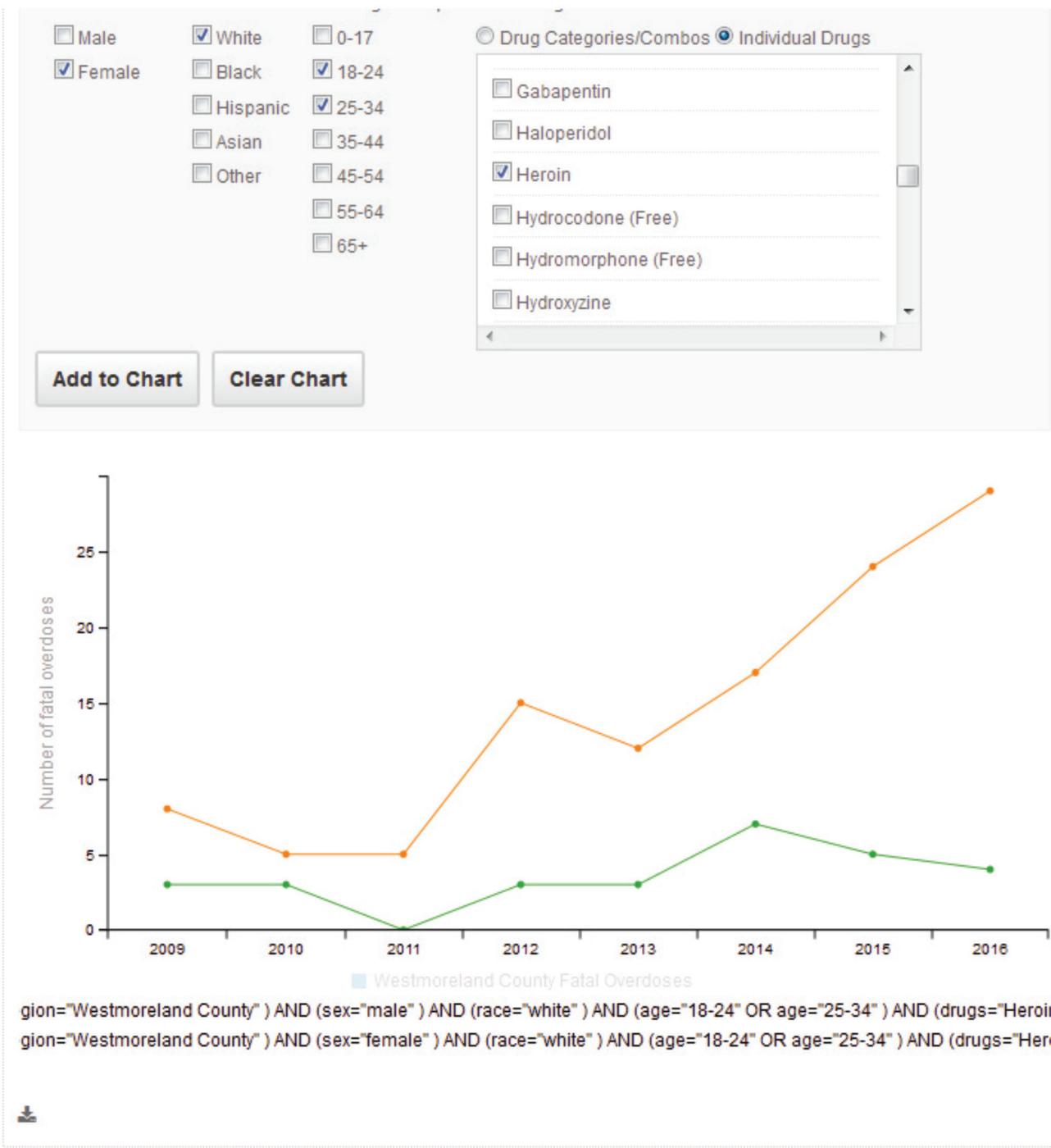


Figure 8: Screenshot showing experience in Westmoreland County of heroin overdoses in the white male and female populations between the ages of 18 and 34.

The chart illustrates a comparison in the frequency of heroin overdose among 18- to 34-year-old white males and females in Westmoreland County, PA. At a glance, the chart communicates an alarming sex-specific increase in heroin-related deaths occurring in males, beginning in 2011.

CONCLUSION

The OverdoseFreePA website is a tool created to provide the most current and specific knowledge of the current addiction and overdose epidemic, such that it serves as a surveillance tool. The data on the site are made available in conjunction with other information, including discussion of potential solutions. The current crisis exists at all jurisdictional levels, but it starts at, and is most intimate at, the local level. As the name suggests, OFPA exists first and foremost as an effort to assist these local communities in the Commonwealth of Pennsylvania.

Two primary community services are provided by OFPA, aside from the previously described overdose death website. One is to provide a broad source of up-to-date educational and other resources for various stakeholders in the law enforcement, rehabilitation, educational, and public health communities (e.g., a list of current naloxone providers in the Commonwealth). The other service, created by the School of Pharmacy of the University of Pittsburgh, is the previously mentioned TAC, which provides conceptual and practical tools for the individual counties in the Commonwealth in dealing with the crisis in their communities.

The previously described arrangement at the ACOME, in which both toxicology and drug chemistry services are housed in the same location, allows for a more completely integrated investigation of the implicated drugs and circumstances surrounding the death, allowing for more accurate certification of the cause and manner of death. The arrangement is optimal, and a desirable standard to emulate on a broader scale.

Without denying the epidemiologic significance of aggregate data at all geographic and jurisdictional levels, having the most current data possible is essential to

keep abreast of the overdose epidemic, as such a system offers the closest thing to real-time surveillance. The standardization of data required by the website may also yield additional benefits for the critically important activity of death certification. The foundation for an epidemiologic basis for assessing the current overdose crisis is accurately classified data, which stems from standardized protocols for determination of incidents of drug overdose.

It is hoped that this article provides an example of a data-driven approach to the current overdose crisis, as well as a format for others to emulate and improve. OverdoseFreePA is committed to sharing ideas and approaches and welcomes feedback, contribution, and collaboration from other like-minded entities.

REFERENCES

- 1) National Institute on Drug Abuse [Internet]. Rockville (MD): National Institute on Drug Abuse; c2016. Overdose death rates; [updated 2015 Dec; cited 2016 Dec 20]. Available from: <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>.
- 2) Centers for Disease Control and Prevention [Internet]. Atlanta: Centers for Disease Control and Prevention; c2016. Injury prevention & control: opioid overdose. Understanding the epidemic; [updated 2016 Dec 16; cited 2016 Dec 19]. Available from: <https://www.cdc.gov/drugoverdose/epidemic/>.
- 3) CDC Wonder [Internet]. Atlanta: Centers for Disease Control and Prevention; c2016. Multiple cause of death data; [reviewed 2016 Dec 8; cited 2016 Dec 20]. Available from: <https://wonder.cdc.gov/mcd.html>.
- 4) Percent of drug poisoning deaths that mention the type of drug(s) involved, by state: 2013–2014 [Internet]. 1 p. Available from: https://www.cdc.gov/nchs/data/health_policy/unspecified_drugs_by_state_2013-2014.pdf.
- 5) Davis GG; National Association of Medical Examiners and American College of Medical Toxicology Expert Panel on Evaluating and Reporting Opioid Deaths. National Association of Medical Examiners position paper: recommendations for the investigation, diagnosis, and certification of deaths related to opioid drugs. *Acad Forensic Pathol*. 2013 Mar; 3(1):77–83. <https://doi.org/10.23907/2013.011>.
- 6) Allegheny County Overdose Prevention Coalition [Internet]. Pittsburgh: the Coalition; 2016 [updated 2016 Aug 12; cited 2016 Dec 24]. Available from: <http://www.acope.pitt.edu/>.
- 7) OverdoseFreePA [Internet]. Pittsburgh: University of Pittsburgh, Program Evaluation and Research Unit; 2016 [cited 2016 Dec 15]. Available from: <http://www.overdosefreepa.pitt.edu>.
- 8) Pringle J. The Pennsylvania Heroin Overdose Prevention Technical Assistance Center manual. Pittsburgh: University of Pittsburgh, Program Evaluation and Research Unit; 2016 [cited 2016 Dec 20]. 106 p. Available from: http://www.overdosefreepa.pitt.edu/tac-training-materials-2/tac-manual_20160711_v3-0/.
- 9) Gill JR. From death to death certificate: what do the dead say? *J Med Toxicol*. 2016 May 2. [Epub ahead of print]. PMID: 27139707. <https://dx.doi.org/10.1007/s13181-016-0551-y>.



- 10) Harruff RC, Couper FJ, Banta-Green CJ. Tracking the opioid drug overdose epidemic in King County, Washington using an improved methodology for certifying heroin related deaths. *Acad Forensic Pathol.* 2015 Sep; 5(3):499-506. <https://doi.org/10.23907/2015.055>.
- 11) Ellis AD, McGwin G, Davis GG, Dye DW. Identifying cases of heroin toxicity where 6-acetylmorphine (6-AM) is not detected by toxicological analyses. *Forensic Sci Med Pathol.* 2016 Sep; 12(3):243-7. PMID: 27114260. PMCID: PMC4967084. <https://dx.doi.org/10.1007/s12024-016-9780-2>.
- 12) Mertz KJ, Janssen JK, Williams KE. Underrepresentation of heroin involvement in unintentional drug overdose deaths in Allegheny County, PA. *J Forensic Sci.* 2014 Nov; 59(6):1583-5. PMID: 25041514. <https://dx.doi.org/10.1111/1556-4029.12541>.
- 13) Williams KE, Freeman MD. The investigation of a cluster of fentanyl overdose deaths: how the use of epidemiologic surveillance and outbreak methods resulted in the rapid identification of the source of a public health crisis. *Acad Forensic Pathol.* 2014 Nov; 4(Suppl): S-4.



The Utility of a Prescription Monitoring Program in Death Investigation: The Virginia Experience

Amy M. Tharp-Myers, Kathrin Hobron, Ralph Orr

ABSTRACT

The Virginia Prescription Monitoring Program (VPMP) has been in effect since 2002, providing reports for prescribers, pharmacists, and other stakeholders in the growing opioid epidemic. The Office of the Chief Medical Examiner is one such stakeholder and has found great efficacy in the program in investigating suspected drug-related deaths. This review examines the origins of the VPMP, its benefits, and limitations for use during death investigation. *Acad Forensic Pathol.* 2017 7(1): 73-79

AUTHORS

Amy M. Tharp-Myers MD, Virginia Office of the Chief Medical Examiner

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

Kathrin Hobron MPH, Virginia Office of the Chief Medical Examiner

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of a related study listed in the citations.

Ralph Orr BS, Virginia Department of Health Professions - Prescription Monitoring Program

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of a related study listed in the citations.

CORRESPONDENCE

Amy M. Tharp-Myers MD, 6600 Northside High School Rd., Roanoke VA 24019, amy.tharp@vdh.virginia.gov

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Prescription monitoring program, Opioids, Medical examiner, Coroner, Death investigation

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.008>

Submitted for consideration on 5 Dec 2016. Accepted for publication on 6 Jan 2017

INTRODUCTION

The current heroin crisis in the United States largely has its origins in prescription opioid abuse. The abuse of opiates or opioid substances for the purposes of euphoria require ever increasing doses to achieve the “high” while increasing the risk of the respiratory depressant effects, for which there is no tolerance. Every day, physicians are tasked with the challenge of determining how best to treat their patients, which may include prescribing controlled and potentially addictive substances. It may be difficult, if not impossible, to determine who is a “drug-seeker” and who has legitimate physical pain (which may be one and the same person). Prescription monitoring programs can assist in reviewing a patient’s prescription drug habits in an objective format. Medical examiners and coroners are also tasked with determining what role, if any, that medications or drugs played in the person’s death. Toxicology results cannot be interpreted without putting them into the context of a specific case; what is lethal in one person may not be lethal in another. The Office of the Chief Medical Examiner of Virginia (OCME) utilized the Virginia Prescription Monitoring Program (VPMP) to facilitate death investigation in the deaths that fall under its jurisdiction.

DISCUSSION

History of the Virginia Prescription Monitoring Program

The mission of the Virginia Prescription Monitoring Program is

To promote the appropriate use of controlled substances for legitimate medical purposes while deterring the misuse, abuse, and diversion of controlled substances (1).

In 2002, the Virginia General Assembly passed legislation that established a pilot program covering counties of the southwestern region of the state, which traditionally had the highest rates of prescription drug abuse and overdose. The region included 29 counties and 12 cities, covered 18% of the state’s population,

and involved approximately 310 pharmacies and 200 000 prescriptions annually (2). Within three years, the number of reports of alleged drug diversion by patients (through doctor shopping, fraud, or forged prescriptions) and prescribers received by the state’s drug diversion unit of the Virginia state police had decreased by 47% in the program area while increasing across other regions of the state. An advisory committee reviewing the preliminary results determined that this established the need for a statewide system as well as allowing access for pharmacists, including all schedule II-IV medications and allowing for unsolicited reports to prescribers when the program managers identified patterns of behavior by patients to indicate doctor shopping or drug diversion. All recommendations were accepted by the General Assembly in 2005 and the system became a true state system. Within one year (from 2005-2006), the number of queries to the system increased from 1773 to 6333, which again more than quadrupled the following year to 22 156 (2).

Currently, 49 states, the District of Columbia, and territory of Guam all have prescription monitoring programs in place or in development, and many systems are beginning to develop interstate sharing of data (3). The sharing of data across state lines is promoted to stop patients from crossing state lines to obtain multiple prescriptions from different prescribers and pharmacies. Prior to these agreements being in place, it was impossible for a prescriber in Virginia to see any prescriptions on the report except those filled at a Virginia pharmacy. Since agreements have been in place with most neighboring states as well as many non-neighboring states, the “border-hopping” behavior can clearly be seen and identified by prescribers using the VPMP. The system includes all schedule II-IV drugs and “drugs of concern” identified by the Board of Pharmacy (which currently includes tramadol).

In 2015, automated registration of all prescribers and pharmacists with active licenses in Virginia occurred, more than doubling the number of registered users. There are requirements for all prescribers who expect opioid treatment to last longer than 14 days to query the system, and pharmacists must enter all medication records within seven days of dispensing the medication.



Of the various programs available in the United States, 41 provide the authority for some access by the medical examiner/coroner system. In 2005, as the Virginia system prepared to expand statewide, the code section (§ 54.1-2523 C. 6.) pertaining to confidentiality of the system allowed the “designated employees” of the Office of the Chief Medical Examiner to obtain information “relevant to determination of the cause of death of a specific recipient” (4). The VPMP has become an invaluable resource during death investigations in multiple ways.

The Office of the Chief Medical Examiner and Drug Deaths in Virginia

In 1946, the General Assembly abolished the coroner position and established the role of Chief Medical Examiner, with the OCME officially becoming a part of the Virginia Department of Health in 1950. Pursuant to Section 32.1-283 of the Code of Virginia, the OCME jurisdiction includes any death from trauma, injury, violence, or poisoning attributable to accident, suicide, or homicide; sudden deaths to persons in apparent good health or deaths unattended by a physician; deaths of persons in jail, prison, or another correctional institution, or in police custody (this includes deaths from legal intervention); deaths of persons receiving services in a state hospital or training center operated by the Department of Behavioral Health and Developmental Services; the sudden death of any infant; and any other suspicious, unusual, or unnatural death (5). The system is divided into four districts (Central, Northern, Tidewater and Western) based on population. The Western district comprises 34 counties, 16 cities, and borders four different states (West Virginia, Kentucky, Tennessee, and North Carolina).

In 2015, drug-related deaths occurred in 1028 persons in Virginia and based upon the first half of 2016, the number of fatal overdoses for all of 2016 is expected to increase by nearly 25% (6). Prior to 2013, the Western District typically received a third of the state’s drug deaths (despite covering a quarter of the state’s population), but in 2013, this began to even out across districts due to the ever increasing heroin and, more currently, illicit fentanyl epidemics. Prior to 2014,

prescription drug deaths occurred most frequently in rural areas (Western District) and fatal illicit opioid overdoses occurred in urban areas.

In 2014 (the most recent complete available data), a total of 992 drug deaths occurred, 511 of which were caused solely by prescription drugs and 182 were “mixed” category (often a combination of prescription and over-the-counter or prescription and illicit drugs). The remainder of cases predominantly involved illicit drugs, with rare cases involving heavy metals, over-the-counter drugs alone, or inhalants. In all drug deaths that year, narcotics were the most commonly detected drug category in toxicology results (present in 35.5% of all drug deaths, 1309 individual narcotic drugs detected). Anti-anxiety (627) and anti-depressant (413) medications were the next most common drug types detected. Alprazolam was present in 6.9% of all drug deaths, representing the most common anti-anxiety medication. Citalopram (2.0%), fluoxetine (1.5%), and trazodone (1.5%) were the most common antidepressant medications detected. Diphenhydramine (active ingredient in many over-the-counter allergy or sleep aid medications) was present in 3.0% of all drug deaths (7).

The most common narcotic detected was morphine (322 instances, 8.9% of cases), with 6-acetylmorphine also detected in 159 instances (4.3%) indicating heroin usage. It is uncertain what percentage of the morphine cases without detectable 6-acetylmorphine represent heroin usage (due to prolonged hospitalization with lack of admission samples or unavailability of urine or vitreous samples hampering interpretation). Of the 163 cases positive for morphine without clear heroin metabolite (6-acetylmorphine), 11 were positive for codeine. Eight of these 11 had a morphine-to-codeine ratio greater than one and circumstances suggestive of heroin (8). Also, beginning in 2014, the Virginia OCME started tracking cases that were thought to be heroin-related based on scene investigation and history regardless of the detection of 6-acetylmorphine. Of the cases that were positive for morphine (but not 6-acetylmorphine or codeine), 23 were thought by the pathologist to be due to heroin based on scene investigation or history.

Oxycodone (196 instances, 5.3%), fentanyl (133 instances, 3.6%), methadone (112 instances, 3.0%) and hydrocodone (96 instances, 2.6%) were the most common prescription narcotics after morphine. During the time period in this report (calendar year 2014), various illicit forms of fentanyl became available in a powdered street version, which was being sold as heroin in many instances. It is uncertain how many of the 2014 fentanyl cases were from this illicit powdered form of fentanyl and how many from use/abuse of prescription fentanyl patches; this problem became even more apparent in 2015 when most fatal fentanyl overdoses statewide were due to illicitly produced versions of the drug. Beginning in 2016, the OCME began categorizing the suspected origin of fentanyl (i.e., illicit, prescription, or unknown) in fatal fentanyl overdoses (9).

In 2015, the total number of drug deaths was highest in large population centers (around Richmond City, Northern Virginia, in the Washington, D.C. suburb communities, and in the Tidewater district around

Norfolk and Virginia Beach). However, when rates by population are determined, the southwestern region (along the Appalachian and Blue Ridge regions) has very high rates compared to other regions (**Figure 1**). The highest rates (per 100 000 population) in the state occurred in Dickenson County (45.6, western district), Winchester (40.0, northern district), Buchanan County (39.2, western district), Patrick County (37.9, western district), and Warren (36.1, northern district). The western counties with the highest rates are predominantly rural and coal-producing parts of the state.

In 2015, one or more prescription opioids (excluding fentanyl) caused or contributed to 38.7% of all fatal drug overdoses in Virginia (6). This percentage has been higher in previous years, before the onset of the heroin and illicit fentanyl epidemic. White males aged 35-54 had the highest rate of fatal prescription opioid overdoses when compared to other demographic groups. This group often falls into the jurisdiction of the OCME due to unclear cause and manner of death (natural disease vs. drugs). Many families of the men

Rate of Fatal Drug Overdose by Locality of Injury, 2015

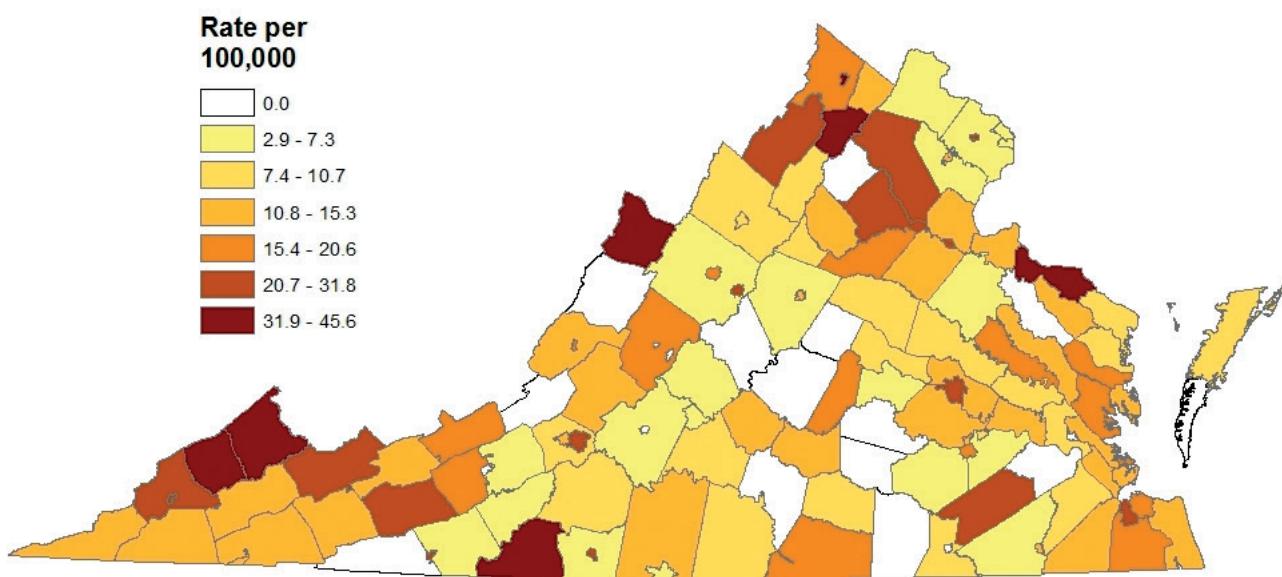


Figure 1: The rate of fatal drug overdose by locality. Counties in the southwestern portion of the state have some of the highest rates of overdose, with large numbers involving prescription medications.

of this age range do not know their medical history and can often provide only sketchy details of their medical treatment or medications. Not having the basic medical history when beginning a death investigation is akin to trying to put together a puzzle with only half the pieces. One may be able to figure out what the picture is supposed to be, but one is just as likely to misinterpret what one is seeing at the autopsy table or in supplemental test results.

The OCME and Use of the Prescription Monitoring Program

Since 2008, the Western District of the OCME queries the VPMP on all deaths accepted under their jurisdiction. The system is occasionally queried as well to determine if patients are truly “unattended” by a physician in the year preceding their death, as families and

friends may not be able to tell law enforcement if the decedent had a physician. The VPMP provides information on any prescription of a controlled substance filled during the requested time frame. The VPMP received more than 4.8 million requests for records in 2015 (**Figure 2**), with the OCME representing 0.15% of those requests (7260 requests) (**Figure 3**) (10). The query is done by medicolegal death investigators upon acceptance of a case under the Medical Examiner’s jurisdiction. The standard request is for any controlled medications prescribed during the year preceding the decedent’s death. This allows for medical records to be requested as soon as possible and, in this day and age of electronic medical records, often facilitates records being received and available for review by the pathologist prior to the autopsy. All Western OCME investigators are certified by the American Board of Medicolegal Death Investigation and are familiar with

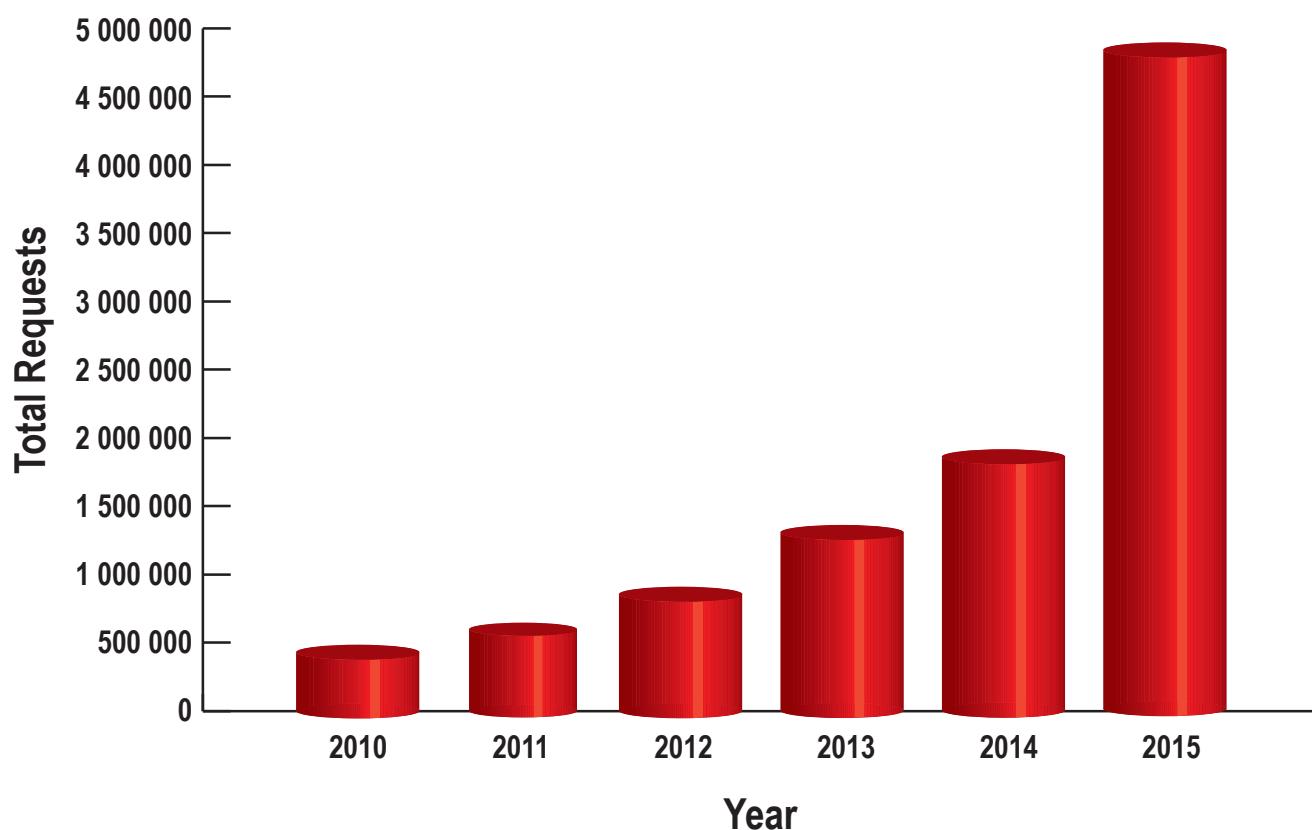


Figure 2: Total requests for reports from the Virginia Prescription Monitoring Program. Interoperability with other state systems, which largely took effect in 2015, has greatly increased the number of requests.

the different drug classes and commonly abused medications. Pathologists also query the system if they wish to expand the search time frame or if records from neighboring states need to be searched.

The VPMP report provides not only a list of all prescriptions filled, but the name of the physician who wrote the prescription, the pharmacy at which it was filled, when it was filled, and for how many doses. It also provides the patient's morphine equivalent daily dose (MEDD). Many studies have shown increased risk of opioid overdose in patients receiving a MEDD greater than or equal to 100 mg/day, particularly in patients who have already experienced a prior overdose event (6, 11-13).

Every pathologist faced with reviewing toxicology reports knows the frustration of looking at a number and attempting to determine its role in the patient's death. While quick references with therapeutic and lethal ranges are helpful, there is often a significant overlap in what is considered lethal and what is not. It is vital that the toxicology results be interpreted in light of the specific patient's history and circumstances, including death scene investigation and their medical and prescription history. The VPMP is often the best resource the OCME has to determine a patient's prescription history so that tolerance can be considered as well as possible drug interactions and combined drug toxic effects.

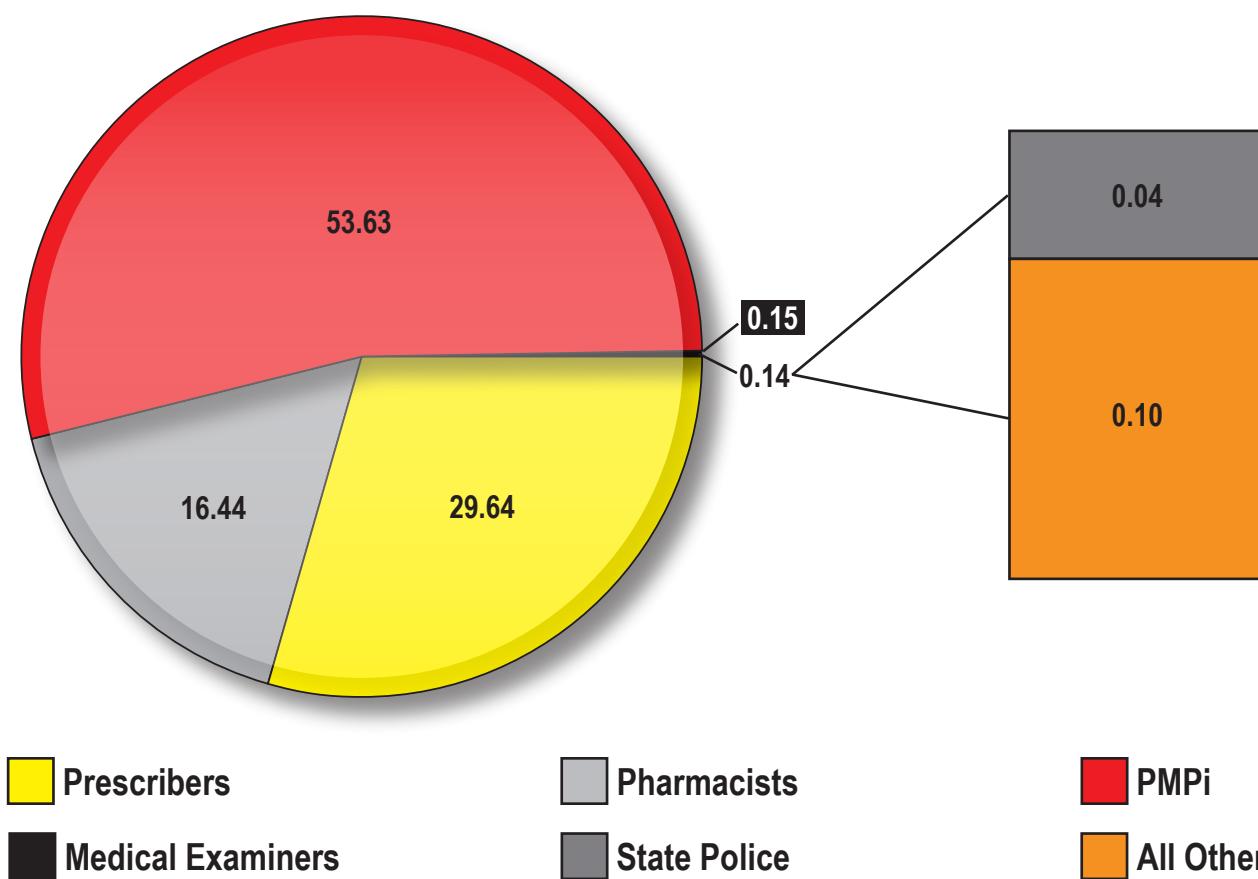


Figure 3: The Office of the Chief Medical Examiner of Virginia accounts for 0.15% of all queries to the Virginia Prescription Monitoring Program. The interoperability (PMPi) with other states accounts for the largest number of queries to the system.



It also allows us to utilize our toxicology testing effectively. Toxicology testing is often costly, time consuming and adds significant delays to turnaround time, frustrating families and law enforcement alike. Being able to review a patient's medication history can give us a head start on what medications and drug classes we should look for first. It also can save toxicology testing altogether if the patient has no drug history, nothing suspicious at the scene, and no controlled substances are prescribed to them. The VPMP also provides a quick reference of which physicians the decedent has seen in the previous year (or longer if requested), providing the medicolegal death investigators a fast route to collecting medical records without having to directly contact grieving families.

CONCLUSION

It is not unusual that OCME is referred a case in which there is initially no suspicion of overdose by scene investigation but the VPMP indicates that the decedent has been prescribed numerous controlled substances from multiple doctors, frequently a combination of pain clinics, ER visits, and dentist visits and are getting their prescriptions filled at multiple pharmacies. This can prompt toxicology testing that might otherwise not have been done. The VPMP has become an invaluable resource to guide our testing and interpretation of results to achieve the most accurate cause and manner of death determinations.

REFERENCES

- 1) Orr RA. Virginia's prescription monitoring program: promoting management, reducing risk [Internet]. Henrico (VA): Virginia Department of Health Professions; 2010 May 1 [cited 2016 Dec 5]. 18 p. Available from: https://www.dhp.virginia.gov/dhp_programs/pmp/docs/May2010/PMPpresentationUVAConf5-1-10.pdf.
- 2) Orr RA. Virginia's prescription monitoring program: 2002-2007 and beyond [Internet]. Henrico (VA): Virginia Department of Health Professions; 2007 Nov 16 [cited 2016 Dec 5]. 21 p. Available from: https://www.dhp.virginia.gov/dhp_programs/pmp/docs/Virginia%27s%20PMP%202002-2007%20and%20Beyond.pps.
- 3) Compilation of Prescription Monitoring Program Maps [Internet]. Manchester (IA): National Alliance for Model State Drug Laws; 2016 May [cited 2016 Nov 8]. 34 p. Available from: <http://www.namsdl.org/library/CAE654BF-BBEA-211E-694C755E16C2DD21/>.
- 4) 2006 Code of Virginia § 54.1-2523 - Confidentiality of data; disclosure of information; discretionary authority of Director.
- 5) 2014 Virginia Code Title 32.1 - Health § 32.1-283. Investigation of deaths; obtaining consent to removal of organs, etc.; fees.
- 6) Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011 Apr 6; 305(13):1315-21. PMID: 21467284. <https://dx.doi.org/10.1001/jama.2011.370>.
- 7) Hobron K. Office of the Chief Medical Examiner's Annual Report, 2014. Richmond: Virginia Department of Health; 2014 [cited 2016 Dec 5]. 263 p. Available from: <http://www.vdh.virginia.gov/content/uploads/sites/18/2016/04/Annual-Report-2014-FINAL.pdf>.
- 8) Davis GG; National Association of Medical Examiners and American College of Medical Toxicology Expert Panel on Evaluating and Reporting Opioid Deaths. National Association of Medical Examiners position paper: recommendations for the investigation, diagnosis, and certification of deaths related to opioid drugs. *Acad Forensic Pathol*. 2013 Mar; 3(1):77-83.
- 9) Hobron K. Fatal drug overdose quarterly report. Edition 2016.2 [Internet]. Richmond: Virginia Office of the Chief Medical Examiner; 2016 Oct [cited 2016 Dec 5]. 28 p. Available from: http://www.vdh.virginia.gov/content/uploads/sites/18/2016/04/Quarterly-Drug-Death-Report-FINAL_10.2016.pdf.
- 10) Orr RA. Virginia prescription monitoring program annual statistics, 2015. Henrico (VA): Virginia Department of Health Professions; 2016 [cited 2016 Nov 14]. 3 p. Available from: https://www.dhp.virginia.gov/dhp_programs/pmp/docs/ProgramStats/2015PMPStatsFinal.pdf.
- 11) Laroche MR, Liebschutz JM, Zhang F, et al. Opioid prescribing after nonfatal overdose and association with repeated overdose. *Ann Intern Med*. 2016 Jan 5; 164(1):1-9. PMID: 26720742. <https://dx.doi.org/10.7326/M15-0038>.
- 12) Dilokthornsakul P, Moore G, Campbell JD, et al. Risk factors of prescription opioid overdose among Colorado Medicaid beneficiaries. *J Pain*. 2016 Apr; 17(4):436-43. PMID: 26721613. <https://dx.doi.org/10.1016/j.jpain.2015.12.006>.
- 13) Zedler B, Xie L, Wang L, Joyce A, et al. Risk factors for serious prescription opioid-related toxicity or overdose among Veterans Health Administration patients. *Pain Med*. 2014 Nov; 15(11):1911-29. PMID: 24931395. <https://dx.doi.org/10.1111/pme.12480>.



County Coroners and Their Role in the Heart of the Opioid Epidemic

Renee Robinson

ABSTRACT

As drug- and opiate/opioid-related deaths continue to rise in the Midwest, we must look at how the type of death investigation in these areas is affected and taxed by the increase. Many states with a large rural component rely on a local coroner system, where death investigation lacks uniformity and requirements for coroner investigative personnel are extremely variable. This has mixed implications for communities and potentially affects law enforcement and prosecution, data collection, and public policy. Both coroner and medical examiner systems benefit from strong leadership, properly trained personnel, and fiscal support. However, operational differences amongst jurisdictions should be addressed so that all stakeholders ultimately receive optimal data. This paper discusses the coroner system of death investigation in one Midwest state (Ohio) in the context of the region's burgeoning opiate/opioid epidemic and suggests opportunities for improvement. *Acad Forensic Pathol.* 2017 7(1): 80-86

AUTHOR

Renee Robinson MD, Stark County Coroner

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

CORRESPONDENCE

Renee Robinson MD, 4500 Atlantic Blvd NE, Canton OH 44705, rmrobinson@neomed.edu

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The author, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The author has indicated that she does not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Opiates, Opioids, Coroners, Medical examiners, Ohio

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.009>

Submitted for consideration on 3 Jan 2017. Accepted for publication on 27 Jan 2017

INTRODUCTION

The Rust Belt and Opiates/Opioids

Since the year 2000, the number of opiate/opioid-related drug overdose deaths has increased significantly (200%), with several states showing a sharp increase. Regions such as New England and the Midwest have been affected particularly hard (**Figure 1**) (1). Both regions have seen an increase in the number of synthetic opioid overdoses (especially fentanyl), but the Midwest, and in particular Ohio, has seen a local acute rise in those that are novel and increasingly toxic, such as carfentanil, which is roughly 100 times more potent than fentanyl, 10 000 times more potent

than morphine, and often arrives from illicit overseas shipments (2).

A multifactorial problem, opiate addiction has been attributed to physician over-prescription, either in response to treating the “fifth vital sign” and the hospital performance measurements attached to that (3, 4), or having been falsely reassured that opiates were non-addictive (5-8), or drug company misconduct (e.g., aggressive marketing; wholesale, targeted mega-shipments [9, 10]). Combined with an influx of potent and cheap street synthetics and semisynthetics and stricter prescribing regulations, many opioid users have found themselves in dangerous and ever-evolving drug territory.

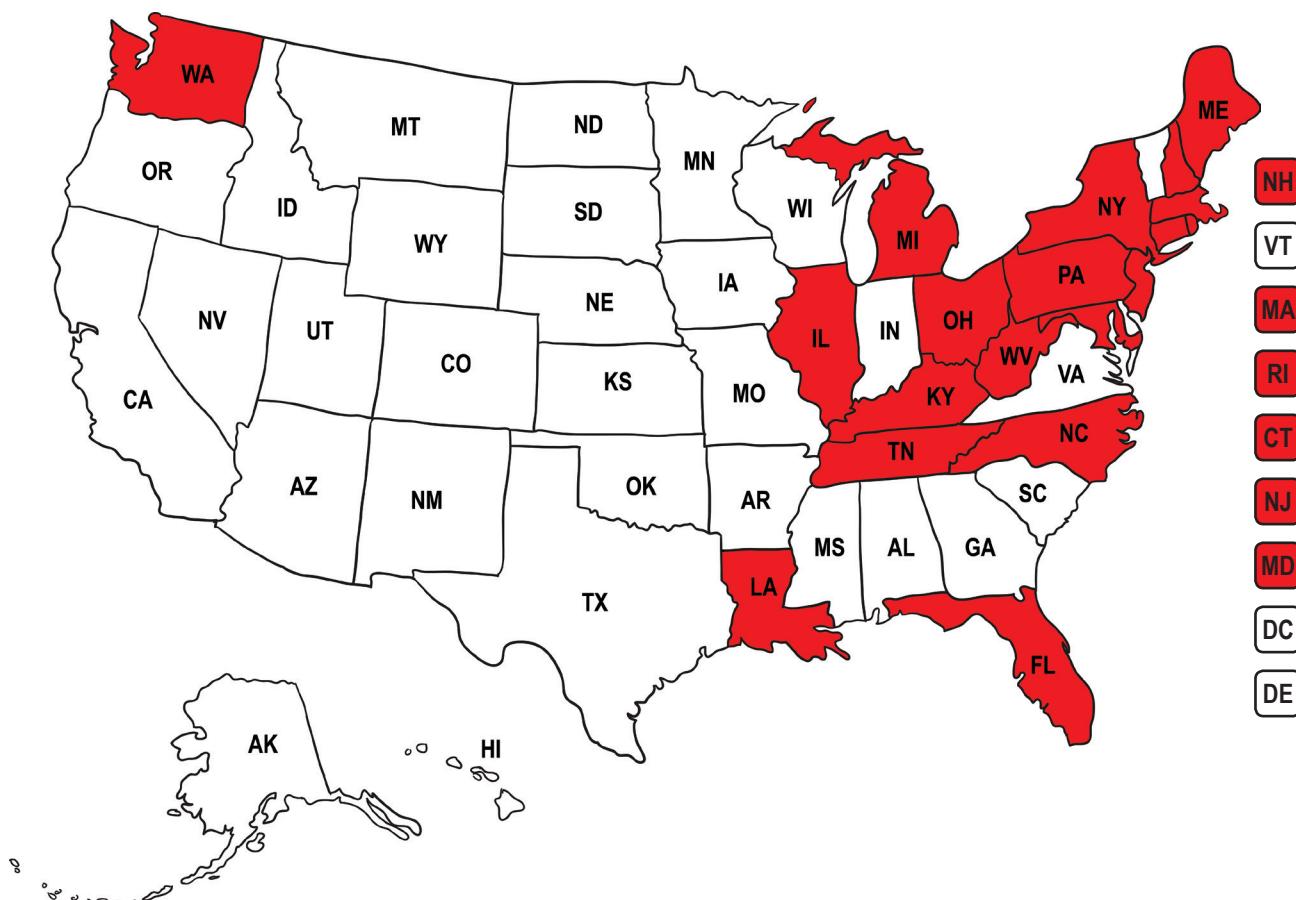


Figure 1: States (in red) denoting a statistically significant increase in drug overdose death rates from 2014 to 2015. Adapted from (11) utilizing “Cartoon USA map” vector image used under license from www.shutterstock.com.

Coroner System in Ohio

The state of Ohio has a mixed medical examiner/coroner (ME/C) system, but with a coroner predominance; of its 88 counties, 86 are overseen by its own independently elected coroner (12). The two remaining counties, Cuyahoga and Summit, have medical examiner's offices, headed by forensic pathologists as appointed by their county's charter government; both are relatively recent conversions from the coroner system (2009 and 1997, respectively) (**Figure 2**).

The other counties maintaining a county coroner, who, as stated by Ohio Revised Code (ORC), are required to be physicians (MD or DO) of any specialty, licensed in the state of Ohio for at least two years prior to assuming the position, and reside within the county they serve (13). Coroners are elected to four-year terms, and there are no term limits. Requirements prior to taking office include 16 hours of continuing education through the state's Coroner association, as well as 16 hours within 90 days of taking office. Throughout the four-year term, an additional 32 hours



Figure 2: Counties served by coroners (no color) versus medical examiner (yellow).

are required. Ohio Revised Code mandates that cause of death (COD) and manner of death (MOD) are to be determined by the coroner (13).

Many counties staffed by a nonpathologist or nonforensic pathologist (FP) coroner often contract with a neighboring county that can provide autopsy services. Coroners without an FP often triage cases, sending only suspicious cases for autopsy while the coroner or his/her investigator/designee performs external exams on the remaining cases. Most FPs are located within major cities and as such, the surrounding counties benefit from their proximity (14) (**Figure 3**). Counties contracting with other counties is often fluid, as resources, funding, or other extenuating circumstances require the shift. Moreover, some counties on the



Figure 3: Regional service provided by forensic pathologists (FP): Counties like Montgomery [15] (in pink), Lucas (purple), Cuyahoga (in yellow), Franklin (blue), Hamilton (grey), Licking (dark green), Summit (in green) Stark (in orange) provide regional service, covering their home counties in addition to surrounding counties. Counties not colored in are contracted with two or more counties. Lorain (light orange), Mahoning (red), and Trumbull (dark purple) cover only themselves. These counties employ only one FP and rely on other counties for coverage when the FP is unavailable.



border of Ohio cover Indiana, Michigan, and Pennsylvania coroner counties. Some individual counties contract with two or more counties for autopsy service coverage.

With the overwhelming increase in opiate/opioid-related deaths, many regional offices with FPs, already taxed by an increased number of drug overdoses within their own counties, have declined to continue contracting with nearby counties to provide autopsy services for drug-related deaths. These counties have either found other, often farther away counties with whom to contract or have decreased the number of overdose cases sent for autopsy.

The epidemic has stretched many jurisdictions' resources and finances, but the coroner system in Ohio (and subsequently, thorough death investigation) may find itself particularly vulnerable, as larger forensic centers decline autopsy coverage. Local coroners have increasingly been asked to assume more complex duties of death investigation with minimal additional training.

DISCUSSION

The baseline pros and cons of medical examiner and coroner systems have been previously discussed in other journal reviews (16), and that discussion is relevant to the roles that these individuals can play in the opioid/opiate epidemic. Looking at the coroner system in Ohio, there are advantages and limitations with regard to the roles that they may play in death investigations and public policy surrounding the drug epidemic.

The Coroner's Role- Advantages

Intrinsic forces that assist the coroner include political influence, which, as discussed below, can be a double-edged sword. With an intelligent, politically active leader, funds can be secured and political alliances forged in the interest of the office's mission, particularly in times of a public health crisis like the opioid epidemic. As an elected official, the coroner is already established in the political landscape and fre-

quently is seen, both by the public and other elected officials, as a medical source expert with regard to issues of mortality. Public support or even discord can work favorably for the office, as public pressure can provide an additional motivation for not just the coroner, but also those in charge of funding the coroner. Politically engaged coroners may be able encourage change in their offices and communities more effectively than a politically disengaged or disinterested medical examiner.

Several coroner's offices directly employ multiple forensic pathologists, some of whom make cause and manner of death determinations upon which the coroner will sign off unchanged.

Extrinsic forces that assist the coroner include election cycles that can provide the community an opportunity to replace subpar leadership or, conversely, ensure continued successful leadership for a set period of time. A forward thinking coroner can run on a platform of opiate awareness.

The Coroner's Role- Limitations

Intrinsic barriers to the coroner investigation refer to those deficiencies inherent to investigations and investigators where training and experience diverge from national standards.

Coroners legally tasked with determination of cause and manner of death may lack formal exposure to proper death certificate phraseology, training in toxicology report interpretation, and other forensic skill sets beyond the basic instruction they receive when they are elected. Some shortcomings these deficiencies may produce include: "laundry list/kitchen sink" approach to death certification, where all drugs positive in the toxicology report are listed; errors of interpretation including failing to identify codeine as a natural occurrence in the poppy plant from which heroin is derived as opposed to an admixed intoxicant; failing to identify additional lethal intoxicants with further toxicologic testing (e.g., fentanyl analogues) or misattributing the COD to another drug or condition when low levels of harmful illicit drugs are present;

or generalization of COD with “multi-drug intoxication” or “drug abuse” without specifying the drug(s) involved. Ohio in particular struggled with death certificate uniformity for drug overdoses, as many coroners did not specifically identify individual drugs on the death certificate, relied solely on hospital record urine screens when admission blood was available for testing, or interchangeably used of the words opiates and opioids, with no distinction between the morphine class and synthetic/semisynthetic derivatives.

For autopsy cases, coroners legally tasked with determination of COD/MOD will take into consideration the FPs report findings, but may find it expedient to reject these findings for a variety of nonscientific reasons. The nature of the coroner’s office is political, and as such, is susceptible to political influence or even grandstanding. For example, a coroner in Pennsylvania has begun ruling all overdose deaths as “homicides” in a misguided attempt to draw attention to the overdose epidemic (17). Others might bend to the will of his/her constituents and their families for political harmony, choosing to ignore findings on MOD or even COD.

For autopsy cases, FPs may not receive adequate information prior to the autopsy, which may affect the direction of the autopsy (e.g., special procedures, collection of additional specimens/evidence).

Some jurisdictions may not have their own independent investigator and may solely rely on police reports. Law enforcement not specifically trained may overlook or misinterpret death scenes where drugs may have played a role.

Some jurisdictions may employ an independent investigator, who may not have had any prior experience, and thus may not be properly trained to triage cases, attend death scenes, or in some cases, perform external examinations.

Extrinsic barriers to the coroner investigation are not dissimilar to some ME offices, but given the nature of small, rural communities, they face issues not seen in larger jurisdictions.

For example, in a rural Ohio county serving roughly 43 000 people, the commissioners allotted the county coroner only three autopsies per year. Remaining cases receive either external examination only or are certified based on medical record review. Ruling drug-related deaths without an autopsy is not endorsed by the National Association of Medical Examiners (18). This practice is not limited to coroner offices; many jurisdictions in Ohio and elsewhere have found it necessary to adopt similar practices due to caseload. The failure to perform an autopsy coupled with a potentially inadequate death scene investigation can only be expected to produce an unacceptable level of erroneous death certifications.

Toxicology itself is often sent out to national laboratories instead of local or in-house labs, with steeper associated costs. The coroner may have to weigh individual tests against cost-benefit in the name of accuracy: does s/he chase 6-monoacetylmorphine in the urine to confirm a heroin overdose? Is an expensive test for carfentanil needed in a person who is already identified as being positive for fentanyl and heroin, but died during a local carfentanil outbreak?

Real-time drug overdose reporting is optimal but difficult for most ME/C offices given the lag inherent to comprehensive toxicology testing. However, smaller, underfunded offices often do not have the software or personnel for timely statistical analysis and dissemination. Public policy and prevention strategy development are thus undermined by inadequate data.

In a jurisdiction with lack of manpower or office space, or rural/travel constraints, toxicology may be drawn on scene, with immediate body release. Interim specimen storage may be subpar.

The Coroner’s Role and the Medical Examiner’s Role

The end game in the opiate epidemic for the ME/C is ultimately data: who is dying from what, and when, and where, and why? On a national level, identification and analysis of fatal epidemics rely heavily on data culled from death certificates. However, if the

root source of data is flawed, this leads to uneven analysis and incorrect conclusions, affecting how those in health care and government approach epidemics and, more importantly, structure aid and resources.

As such, it is imperative that there is some degree of uniformity in the wording of cause of death. This is assuming the investigations to be equal, which may not be the case for aforementioned reasons. Unfortunately, ME/C's cannot control how that data is further processed, however. Reliance on ICD-10 coding of cause of death has somewhat affected how the Centers for Disease Control and Prevention (CDC) reports. In a recent study where CDC researchers utilized not only the cause of death, but also "Part II/Contributory factors" and "How injury occurred" boxes on the death certificate, they found that while the top ten abused drugs did not change, their order of prevalence did (19).

CONCLUSION

In any system, there will never be a perfect death investigation. But the goal is to change what we can to minimize errors on our end. Many changes that would even out a patchwork death investigation system require legislative progressiveness; this sort of change, while welcome, is often cumbersome and slow. As it were, many coroner systems already function similar to regional statewide medical examiner system where several counties' autopsy services are covered by forensic pathologists or even by an adjacent sovereign medical examiner's office. States like California have recently passed legislation to further ensure uniform death investigation, eliminating redundancy and ensuring competency, for example, by allowing forensic pathologists as opposed to lay coroners to rule on cause and manner of death (20).

Expansion and continuation of education for ME/Cs is imperative for the continued evolution of death investigation. Resources are available for self-education on certifying drug-related deaths (21); local and national professional meetings have offered programs and lectures on the importance of thorough death investigation. Open lines of communication between adjacent

counties, cities, and states can allow for exchange of information and trends, and the opportunity to develop consistent investigative practices. Continued education of those not directly working for an ME/C office (e.g., prosecutors, public health agencies, county commissioners or finance directors) is also vital, as it is difficult to advocate for change where there is a fundamental misunderstanding of the job duties and requirements. Likewise, education and consistent communication between prosecutorial elected officials and the ME/Cs can help align expectations in drug death investigations and prosecutions. A prosecutor must understand the limits of an external exam only with toxicology, as the possibility of competing causes of death, or nuance in toxicological testing and interpretation requires a full autopsy for a thorough and accurate COD. Failure to comprehend this necessity can lead to political budgetary antagonism, or at worst, miscarriages of justice.

But ultimately, to effect real change, proper support, resources, and money must be allocated to both big cities and rural districts. The best, most educated coroner cannot effectively perform the job if s/he is the only person serving the county, an all too common occurrence.

As we encounter new drugs, we must consider new tools and ways of investigating. We must assess and reassess our current approaches both in the autopsy room and in the community. We must continue to educate ourselves and those directly/indirectly involved with our offices. We must advocate for appropriate resources for competent death investigation. Finally, we must push for widespread accreditation for both coroner and medical examiner offices, as accreditation is the first step to ensuring competency, and can be used to leverage appropriate funding.

The focus of the article is local to Ohio, and as such, specific to Ohioans and Ohio law. Though many other jurisdictions struggle with the same issues as Ohio, it would be a worthy exercise to investigate the practices of other locales where the elected coroner requires no formal medical, forensic, or even basic educational level, training or continuing education to hold office.



Fatal opiate/opioid overdoses are increasing at an alarming rate. The data that we as forensic professionals collect are instrumental in identifying the drugs harming the community, and we in turn share our findings to the interested parties in the community and government at large. It is imperative that this data is uniform, specific, and accurate.

REFERENCES

- 1) Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths — United States, 2000–2014. *MMWR Morb Mortal Wkly Rep.* 2016 Jan 1; 64(50-51):1378-82. PMID: 26720857. <https://dx.doi.org/10.15585/mmwr.mm6450a3>.
- 2) Kinetz E, Satter R. Ohio is hardest hit by Chinese carfentanil trade, logging 343 of more than 400 seizures in U.S. *Akron Beacon Journal/Ohio.com* [Internet]. 2016 Nov 3 [cited 2017 Jan 3]; Local news: [about 2 screens]. Available from: <http://www.ohio.com/news/local/ohio-is-hardest-hit-by-chinese-carfentanil-trade-logging-343-of-more-than-400-seizures-in-u-s-1.724486>.
- 3) Hanks S. The law of unintended consequences: when pain management leads to medication errors. *P T.* 2008 Jul; 33(7):420-5. PMID: 19750120. PMCID: PMC2740947.
- 4) The Joint Commission [Internet]. Oakbrook Terrace (IL): The Joint Commission; c2017. Joint Commission statement on pain management; 2016 Apr 18 [cited 2017 Jan 3]. Available from: https://www.jointcommission.org/joint_commission_statement_on_pain_management/.
- 5) Plea agreement: *United States of America v. The Purdue Frederick Company, Inc.* 2007 May 10 [cited 2017 Jan 3]. Available from: http://graphics8.nytimes.com/packages/pdf/business/20070510_DRUG_Purdue.pdf.
- 6) Meier B. In guilty plea, OxyContin maker to pay \$600 Million. New York Times [Internet]. 2007 May 10 [cited 2017 Jan 3]. Available from: <http://www.nytimes.com/2007/05/10/business/11drug-web.html>.
- 7) Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med.* 1980 Jan 10; 302(2):123. PMID: 7350425. <https://doi.org/10.1056/nejm198001103020221>.
- 8) Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain.* 1986 May; 25(2):171-86. PMID: 2873550.
- 9) Dhalla IA, Persaud N, Juurlink DN. Facing up to the prescription opioid crisis. *BMJ.* 2011 Aug 23; 343:d5142. PMID: 21862533. <https://doi.org/10.1136/bmj.d5142>.
- 10) Eyre E. Drug firms poured 780M painkillers into WV amid rise of overdoses. West Virginia Gazette Mail [Internet]. 2016 Dec 17 [cited 2017 Jan 3]. Available from: <http://www.wvgazettemail.com/news-health/20161217/drug-firms-poured-780m-painkillers-into-wv-amid-rise-of-overdoses>.
- 11) Centers for Disease Control and Prevention. Atlanta: Centers for Disease Control and Prevention; c2017. Drug overdose death data; 2016 [updated 2016 Dec 16; cited 2017 Jan 3]. Available from: <https://www.cdc.gov/drugoverdose/data/statedeaths.html>.
- 12) Centers for Disease Control and Prevention. Atlanta: Centers for Disease Control and Prevention; c2017. Coroner/medical examiner laws; 2014 Jan 1 [cited 2017 Jan 3]. Available from: <https://www.cdc.gov/phlp/publications/coroner/ohio.html>.
- 13) Ohio Revised Code. Available from: <http://codes.ohio.gov/orc/313> Ohio Revised Code.
- 14) County Advisory bulletin, September 2016 [Internet]. County Commissioners Association of Ohio. Columbus: County Commissioners Association of Ohio; 2016 Sep [cited 2017 Jan 3]. Available from: <https://www.ccao.org/userfiles/CAB%202016-06%20%209-26-16.pdf>.
- 15) Montgomery County Coroner's Office [Internet]. Dayton (OH): Montgomery County; c2016. Contractual autopsy services; [cited 2017 Jan 3]. Available from: http://www.mcohi.org/government/elected_officials/coroner/contractual_autopsy_services.php.
- 16) Hanzlick RL, Fudenberg J. Coroner versus medical examiner systems: can we end the debate? *Acad Forensic Pathol.* 2014 Mar; 4 (1):10-7. <https://doi.org/10.23907/2014.002>.
- 17) Beauge J. Heroin overdoses will now be considered homicides, coroner says. Penn Live [Internet]. 2016 Mar 23 [updated 2016 Jun 22; cited 2017 Jan 3]. Available from: http://www.pennlive.com/news/2016/03/lycoming_county_coroner_listin.html.
- 18) Davis GG; National Association of Medical Examiners and American College of Medical Toxicology Expert Panel on Evaluating and Reporting Opioid Deaths. National Association of Medical Examiners position paper: recommendations for the investigation, diagnosis, and certification of deaths related to opioid drugs. *Acad Forensic Pathol.* 2013 Mar; 3(1):77-83. <https://doi.org/10.23907/2013.011>.
- 19) Warner M, Trinidad JP, Bastian BA, et al. Drugs most frequently involved in drug overdose deaths: United States, 2010-2014. *Natl Vital Stat Rep* [Internet]. 2016 Dec [cited 2017 Jan 3]; 65(10):1-15. Available from: https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_10.pdf.
- 20) California Legislative Information [Internet]. Sacramento: State of California; c2017. SB-1189 Postmortem examinations or autopsies: forensic pathologists; [cited 2017 Jan 3]. Available from: https://leginfo.legislature.ca.gov/faces/billCompareClient.xhtml?bill_id=201520160SB1189.
- 21) Medical examiners' and coroners' handbook on death registration and fetal death reporting. Hyattsville (MD): Centers for Disease Control and Prevention; 2003 Apr [cited 2017 Jan 3]. Available from: https://www.cdc.gov/nchs/data/misc/hb_me.pdf.



Rules for Establishing Causation in Opiate/Opioid Overdose Prosecutions — The Burrage Decision

Thomas P. Gilson, Carole Rendon, Joseph Pinjuh

ABSTRACT

As the opiate/opioid crisis has worsened in the United States, one of the law enforcement responses has involved increased efforts to prosecute the individuals responsible for the distribution of illicit drugs that result in overdoses. When mixed intoxications occur, the controlling decision for prosecution is *Burrage v. United States* (2014), which provides guidance on the types of evidence required for establishment of causation. In many types of legal proceedings, forensic pathologists are called to provide expert testimony, although they may be unaware of the burden of proof that is required in a given case. This paper seeks to elaborate upon the burden of proof in drug overdose prosecutions with the guidance of Burrage and offer insight into the expectations and limitations involved in these cases.

Acad Forensic Pathol. 2017 7(1): 87-90

AUTHORS

Thomas P. Gilson MD, Cuyahoga County Medical Examiner

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

Carole Rendon JD, United States Attorney's Office Northern District of Ohio

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, writing assistance and/or technical editing.

Joseph Pinjuh JD, United States Attorney's Office Northern District of Ohio

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, writing assistance and/or technical editing.

CORRESPONDENCE

Thomas P. Gilson MD, 11001 Cedar Avenue, Cleveland OH, docgilson@msn.com

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Opioid, Prosecution, Intoxication

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.010>

Submitted for consideration on 21 Dec 2016. Accepted for publication on 23 Jan 2017



INTRODUCTION

The United States is in the midst of a significant heroin and opioid epidemic. Given the mortality rates, this epidemic has quickly become the most significant law enforcement and public health crisis we have seen in decades. Prescription opioid pain relievers initially accounted for much of the mortality and continue to remain a major factor in some parts of the country. As law enforcement and the medical community have started to address the issues surrounding the use and misuse of prescription opioids, many jurisdictions, including the Northern District of Ohio, have seen a significant rise in the abuse of illicit narcotics like heroin and clandestinely manufactured fentanyl. As part of the law enforcement response to this crisis, efforts have increased to hold the drug dealers accountable with a special sentence enhancement when their criminal conduct directly results in a fatal or nonfatal overdose by one their customers.

For the past several decades, forensic evidence has become an increasingly important part of the investigation and prosecution of criminal cases, especially in federal court (1). Reliable scientific data has become a cornerstone of the criminal justice system. Yet, often lawyers and scientists do not fully appreciate the requirements and limitations of one another's work (2). Prosecutors must meet an exacting "beyond a reasonable doubt" burden of proof on every element of a charged offense. Those elements, however, vary significantly based on the nature of the crime that has been alleged. As discussed below, the elements the prosecution must prove to seek to impose an enhanced sentence for an overdose include that "but for" the illegal substance the drug dealer sold, the victim would not have died or suffered serious bodily injury. If a substance contributes to death, this does not necessarily imply "but for" causation. The concept of "but for" causation (which has its origins in tort law) would require the substance to be able to stand alone in causation.

DISCUSSION

Burrage v. United States

In the prosecution of drug distribution cases that carry a sentence enhancement for death or serious bodily injury, the controlling decision is *Burrage v. United States* (3). In *Burrage*, the Supreme Court discussed the elements the government must establish beyond a reasonable doubt to hold a defendant liable for causing a drug user's death or serious bodily injury, particularly where an overdose occurs in the context of mixed drug intoxications. This paper summarizes the Supreme Court's decision and offers insights into the types of evidence that must be available to pursue this sentence enhancement.

Burrage involved a drug user named Joshua Banka who died after using a number of illegal drugs over the course of a single day, including marijuana, oxycodone (which he crushed, cooked, and then injected), and heroin (which he also cooked and injected). Marcus Burrage was the drug dealer who sold Banka the heroin. Burrage was tried and convicted for selling only the heroin to the decedent and was held accountable on the theory that Banka's death resulted from using the heroin he purchased from Burrage. Specifically, Burrage's indictment included a charge under Title 21, United States Code, Section 841(b)(1)(C), which provides for a 20-year mandatory minimum sentence where death or serious bodily injury results from the distribution and use of an illegal drug. At trial, the government presented testimony from two medical experts, each of whom was called to testify about the cause of Banka's death. Each testified that the heroin "*was a contributing factor*" in Banka's death (3). Neither expert testified that Banka would have lived if he had not taken the heroin. The jury, however, was instructed that it could convict Burrage of the death specification charge if it found beyond a reasonable doubt that "*the heroin distributed by the Defendant was a contributing cause of Joshua Banka's death*" (3).

The critical question presented to the Supreme Court was whether that jury instruction accurately described what the government was required to prove to estab-

lish, as the statute requires, that Banka's death "resulted from" the heroin that Burrage sold to him. The Supreme Court held that the jury instruction that was given was insufficient and that instead, the government must prove that "but for" the heroin he ingested, Banka would not have died. The Court clarified, however, that the government did not have to prove that the heroin was the only cause of Banka's death; but it must have been the straw that "broke the camel's back" (3). Although it does not have to be the only cause, the evidence must establish that the drug that was sold was "*an independently sufficient cause of the victim's death or serious bodily injury*" (3).

To illustrate the fact that the "but for" causation is not an insurmountable hurdle, and that there can be more than one "but for" cause for an event, Justice Scalia described a hypothetical baseball game in which the visiting team wins by a score of one to zero, with their leadoff batter hitting a home run in the first inning of play. Here, although the home run was a "but for" cause of the victory, it would not be the only necessary cause of the victory because the team would not have won without great defense, great pitching, the coach's decision to give the batter the leadoff spot, and many other factors. In contrast, if the visiting team won the game by a score of five to two, no one would say the leadoff home run was a "but for" cause of the victory – because the team would have won even without that home run. Thus, there can be more than one "but for" cause, but a nonessential factor cannot satisfy the "but for" causation requirement.

Challenges of Mixed Drug Intoxication Cases

As certifiers of causes of death, most medical examiners and coroners are familiar with the concept of "but for" causation. Where a single drug is involved in the lethal intoxication, the issue of causation is more obvious. Challenges arise, however, when more than one intoxicant is present. The Supreme Court in Burrage requires that the supplier be shown to have provided an intoxicant that, in and of itself, would have been fatal or would have caused serious bodily injury (i.e., "but for" that intoxicant, the death or serious bodily injury by overdose would not have occurred).

In mixed drug intoxication scenarios, this standard may be difficult to apply. Several mixed drug intoxications involve combinations of substances, any one of which may have been lethal (e.g., heroin, fentanyl, cocaine, amphetamines). In these instances, it is often not possible for the forensic pathologist to opine with a degree of medical certainty that any one of the substances represents a "but for" cause of death or serious bodily injury. In those cases, consideration should be given to the entire case investigation (e.g., terminal collapse circumstance information, presence of only inactive metabolites of one of the substances) to arrive at a medically appropriate opinion. It is also worth bearing in mind that certain depressant drugs like ethanol or benzodiazepines will potentiate the depressant effects of the opiates/opioids but are not often likely to produce death in and of themselves (4, 5). In a mixed drug intoxication of this type, it may be reasonable to acknowledge the contributory and potentiating effect of the ethanol or benzodiazepine in the cause of death and still regard the opiate/opioid as a "but for" factor in the death even though it does not appear in isolation on the death certificate. Provided the expert can testify that, without the incremental effect of the illegal drug at issue, the decedent would have lived or not suffered serious bodily injury, the prosecution can properly seek the sentence enhancement under the Supreme Court decision on the federal guideline.

CONCLUSION

Forensic evidence, particularly toxicology, is essential to the proper adjudication of drug-related fatalities. It is worthwhile for certifiers of death to understand the Burrage decision and how it impacts the administration of justice in these cases. Enhanced sentencing options of drug dealers in fatal overdose cases present a potentially powerful deterrent to traffickers and the Burrage decision offers a "*reasonable and attainable*" standard for such prosecutions (6). Competent certification, along with unbiased testimony, are the touchstones of justice in these cases.



REFERENCES

- 1) Peterson JL, Hickman MJ, Strom KJ, Johnson DJ. Effect of forensic evidence on criminal justice case processing. *J Forensic Sci.* 2013 Jan; 58 Suppl 1:S78-90. PMID: 23106604. <https://dx.doi.org/10.1111/1556-4029.12020>.
- 2) Roberts P. Paradigms of forensic science and legal process: a critical diagnosis. *Philos Trans R Soc Lond B Biol Sci.* 2015 Aug 5; 370 (1674). pii: 20140256. PMID: 26101282. PMCID: PMC4581001. <https://dx.doi.org/10.1098/rstb.2014.0256>.
- 3) *Burrage v. United States*, 134 S.Ct. 881 (2014)
- 4) Kann D, Brewer RD, Mesnick JB, et al. Vital signs: alcohol poisoning deaths - United States, 2010-2012. *MMWR Morb Mortal Wkly Rep.* 2015 Jan 9; 63(53):1238-42. PMID: 25577989.
- 5) Greenblatt DJ, Allen MD, Noel BJ, Shader RI. Acute overdosage with benzodiazepine derivatives. *Clin Pharmacol Ther.* 1977 Apr;21(4): 497-514. PMID: 14802. <https://doi.org/10.1002/cpt1977214497>.
- 6) Ihlenfeld WJ. "Death Results" prosecutions remain an effective tool post-Burrage. *US Attorneys' Bull.* 2016 Sept; 64(5):45-52.



Common Findings and Predictive Measures of Opioid Overdoses

Danielle E. Pelletier, Thomas A. Andrew

ABSTRACT

Purpose: This research examines autopsy findings from fatal opiate/opioid intoxications in New Hampshire for cerebral edema, pulmonary edema, and urinary bladder distension in the interest of finding predictability of such cases.

Methods: Autopsy reports of 150 decedents, between 20 and 40 years old, were reviewed. Subjects were divided into three groups as follows: 50 whose cause of death was opioid intoxication excluding fentanyl, 50 who died from fentanyl, and 50 who, lacking intoxication, died from cardiac issues, seizure disorders, or positional asphyxia as the control group. Autopsy reports were reviewed for cerebral edema, pulmonary edema, and urinary bladder distension.

Results: Pulmonary edema was present in 96% of those who died of fentanyl alone and in 94% of those who died of opioids excluding fentanyl. Cerebral edema occurred in 54% of decedents who died of opiates/opioids excluding fentanyl and 8% in those who died solely of fentanyl. Thirty-four percent of the fatal intoxications excluding fentanyl had bladder distension while only 16% of those who died of fentanyl intoxication. The control group found 30% had pulmonary edema, 2% had cerebral edema, and none had bladder distension. The triad occurred in 8% of intoxications and never in the control group.

Conclusion: The results validated correlation between opioid intoxication and pulmonary edema, cerebral edema, and bladder distension. Cerebral edema and bladder distension suggest opioid intoxication, but arise less frequently in fentanyl intoxication. We hypothesize that fentanyl causes death more rapidly than other opioids leading to these results. Given the variations, we do not recommend reliance on postmortem computed tomography *in lieu* of autopsy to evaluate potential fatal intoxications. *Acad Forensic Pathol.* 2017 7(1): 91-98

AUTHORS

Danielle E. Pelletier BS, Office of Chief Medical Examiner, State of New Hampshire

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, general supervision, writing assistance and/or technical editing.

Thomas A. Andrew MD, Office of Chief Medical Examiner, State of New Hampshire

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, general supervision, writing assistance and/or technical editing.

CORRESPONDENCE

Danielle E. Pelletier BS, 246 Pleasant Street Suite 218, Concord NH 03301, danielle6elizabeth@gmail.com

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

This work was presented at the 2016 NAME Annual Meeting. The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Opioid, Fentanyl, Pulmonary edema, Cerebral edema, Urinary bladder distension

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.011>

Submitted for consideration on 9 Dec 2016. Accepted for publication on 2 Feb 2017

INTRODUCTION

Deaths from opiate/opioid intoxication has become a nationwide problem that has been drastically increasing in the past five years. Since 2000, deaths from drug overdoses has increased 137% and deaths specifically from opiates/opioids has increased 200% (1). New Hampshire has shown to have one of the highest drug overdose rates in the nation (1). In 2011, 157 of the 201 total deaths from drug intoxication were opiate/opioid-related. In 2015, total drug deaths rose to 439, with 397 being opiate/opioid-related. The New Hampshire Office of the Chief Medical Examiner (OCME) projects based on year-to-date data, that in 2016, opiate/opioid deaths will increase to well over 400 out of the projected 494 total drug deaths (2). Over half of the opiate/opioid deaths in 2015 were caused by fentanyl (**Table 1**).

Fentanyl is a synthetic and short-acting opioid analgesic and is 50-100 times more potent than morphine (3). Pharmaceutical fentanyl is known to be misused, but most cases of fentanyl-related deaths in this medicolegal jurisdiction are from illicitly manufactured fentanyl and fentanyl analogues (3). Nonpharmaceutical fentanyl is produced in clandestine laboratories and often sold in disguise making it that much more dangerous on the streets as consumers of illicit agents often do not know the contents of what they are taking (3).

Fentanyl, like other opiates and opioids, act on opioid receptors that are distributed throughout the body. Highly conserved opioid receptor substrates have been demonstrated in a wide range of systems, from neurons in the hippocampus, locus ceruleus, and ventral tegmental area, to the dorsal root ganglia (4). Evidence has supported the concept that opioid receptors positively couple to potassium channels while also negatively modulating calcium channels in many model systems and cell types (4). This alteration of ion channels within the body and their abundance in the peripheral and central nervous system lead to a variety of physiological effects upon receptor activation. Peripheral effects include constipation, urinary retention, hives, and bronchospasm; central effects consist of nausea, sedation, respiratory depression, hypotension, miosis, and cough suppression (4).

Respiratory depression is one of the biggest concerns in opioid use because it has shown to lead to pulmonary edema. Healthy lungs are the site of fluid and solute filtration that moves by transvascular hydrostatic and protein osmotic pressure differences. In pulmonary edema, the rate of fluid filtration exceeds the rate of lymphatic removal (5). Pulmonary edema is divided into two main types: cardiogenic (or hydrostatic) and noncardiogenic (or increased permeability) (5). Cardiogenic pulmonary edema results from a marked increase in pulmonary capillary hydrostatic pressure, whereas noncardiogenic pulmonary edema follows an increase in the permeability of the endothelium to

Table 1: Number of Deaths and the Drugs Responsible, Per Year

| Opiates/Opioids | Number of Deaths 2011 | Number of Deaths 2012 | Number of Deaths 2013 | Number of Deaths 2014 | Number of Deaths 2015 |
|---|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Fentanyl (no other drugs) | 5 | 5 | 9 | 77 | 161 |
| Fentanyl and other drugs (excluding heroin) | 12 | 5 | 7 | 31 | 78 |
| Heroin (no other drugs) | 21 | 21 | 40 | 40 | 31 |
| Heroin and other drugs (excluding fentanyl) | 23 | 16 | 28 | 20 | 13 |
| Heroin and fentanyl | 0 | 0 | 1 | 38 | 44 |
| Other opiates/opioids | 96 | 74 | 77 | 88 | 70 |
| Total deaths caused by opiates/opioids | 157 | 121 | 162 | 294 | 397 |
| Total drug deaths | 201 | 163 | 192 | 326 | 439 |

fluid and protein (5). Drug-induced pulmonary edema is typically classified as noncardiogenic, but, in fact, shows features of both increased hydrostatic pressure, caused by intense sympathetic stimulation, and increased permeability (5). Drug-induced pulmonary edema can be fatal.

Opioid receptor activation also leads to cerebral edema, with subcellular molecular mechanisms similar to those that produce pulmonary edema. Calcium and sodium ion channels are altered upon activation, causing an accumulation of sodium within the cell and creating an osmotic gradient (6). Cells are flooded with water in response to the change in concentrations and hypoxia depletes cellular energy stores, disabling the sodium-potassium pump (6). This pump failure and the resulting accumulation of sodium causes fluid to move from the extracellular to the intracellular space to maintain osmotic equilibrium, activating intracellular cytotoxic processes (6). This leads to an inflammatory response, creating increased intracranial pressure since the described fluid shifts occur within a rigid environment that does not allow for expansion.

As mentioned above, one of the peripheral effects upon opioid receptor activation is urinary retention. When activated, there is a decreased sensation of bladder fullness by partially inhibiting the parasympathetic nerves involved with the bladder (7). They have also shown to increase the sphincter tone of the urinary bladder by the over-stimulation of the sympathetic nervous system leading to outlet resistance (7). These two working together ultimately lead to urinary retention which, in cases of fatal intoxication, may be seen as a distended bladder in autopsy and postmortem computed tomography (PMCT).

A study published in 2012, by Rohner et al., has shown that urinary bladder distension is much more frequent in cases of fatal drug intoxication than in decedents who were not intoxicated (8). They found a 162.8 mL difference in mean urine volumes between a study group of fatally intoxicated individuals and their control group who had negative toxicology results (8). The authors concluded that they found a positive relationship between intoxication and urinary bladder volumes.

The previous study was supported by another done by Winklhofer et al. published in 2014 that examined whole body PMCT scans of individuals from fatal opioid intoxication in which they found 42% of those intoxicated had a distended bladder (9). The control group found this in only 9.1% of the decedents. This study also showed higher frequencies of pulmonary edema and cerebral edema in the intoxicated individuals. Pulmonary edema was present in 95% of the study group and cerebral edema in 49%. The study saw all three present simultaneously in intoxicated individuals numerous times, but not once in the control group. The triad of cerebral edema, pulmonary edema, and a distended urinary bladder as an indicator of opioid-related deaths had a 26% sensitivity and a 100% specificity, as confirmed by autopsy and toxicology analysis (9).

Past research and these two studies that examine relationships between intoxication and postmortem findings support that these three findings have a strong correlation with opiate/opioid intoxication and encourage further research (**Figure 1**). This study aims to highlight frequent findings and potential predictive measures of opioid overdoses.

METHODS

Subjects were found and collected through query searches from the New Hampshire's Office of Chief Medical Examiner's database.

Each year, the New Hampshire's Office of Chief Medical Examiner tracks all fatal intoxications that occur within the state for that year. This information is used for statistical purposes as well as research. The OCME case file includes the age of the decedent as well as the specific drugs involved in the fatality. Using these statistics, the two study groups for this research were created. Only autopsy cases of fatally intoxicated individuals from 2012 to 2015 were used, for a total of 587 autopsy cases. All decedents younger than 20 and older than 40 were excluded from the study group. The age range was kept narrow to prevent outliers based on varying physiological conditions in the very young and confounding comorbid-

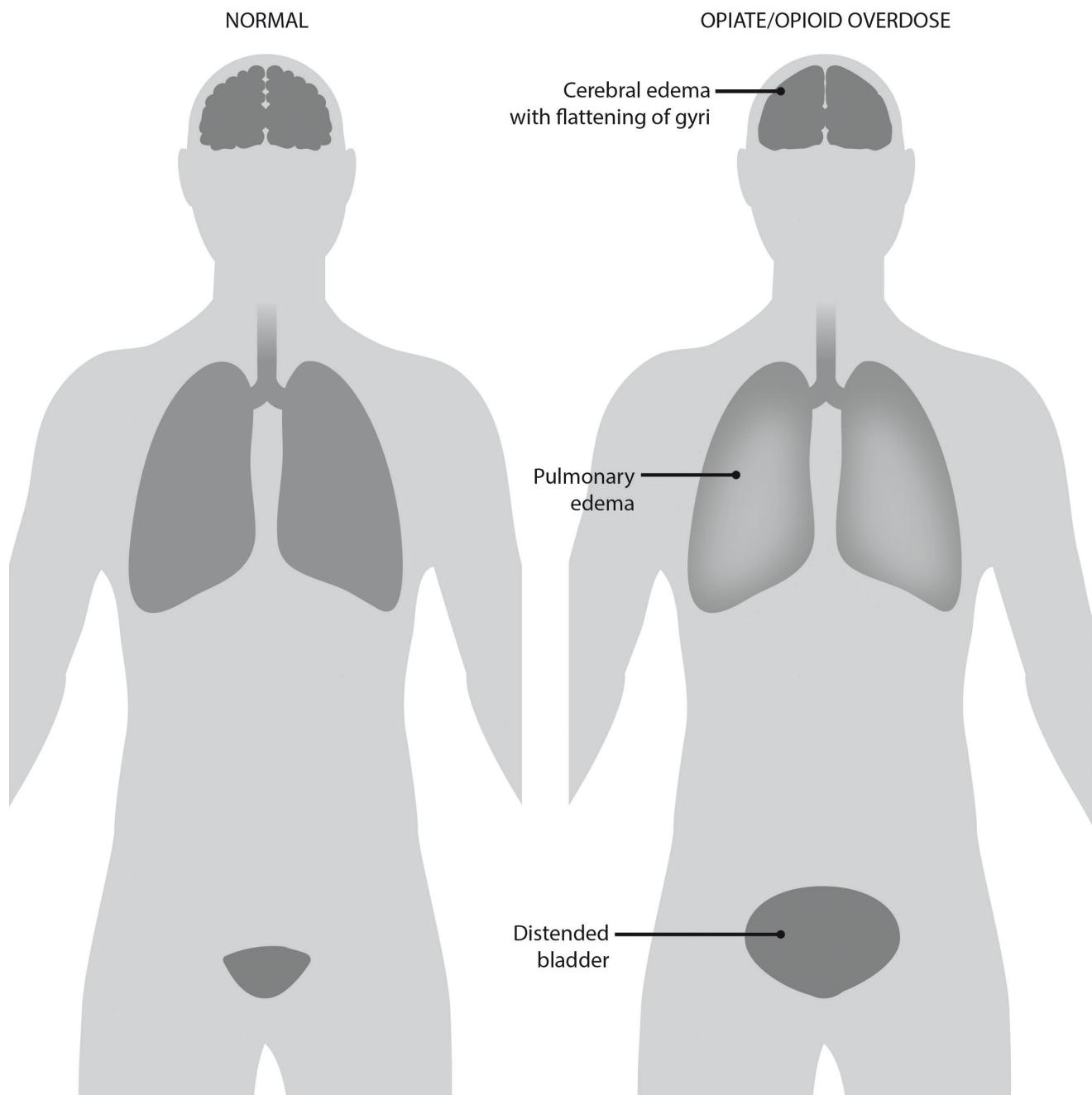


Figure 1: The triad of findings that can be observed in opioid deaths. Created under contract by professional medical illustrator Diana Kryski.

ties in older decedents. This reduced the number of usable cases to 300. The remaining decedents were then separated based on the drugs involved in the cause of death. This research aimed to reveal differences in postmortem changes between those who

died from fentanyl alone and those who died from other opioids excluding fentanyl; therefore, all deaths caused by multiple opioids including fentanyl were excluded from this study. This further reduced the number of cases to 184, leaving 64 decedents who

died of acute fentanyl intoxication and 120 who died from intoxication by another opioid. Fifty cases were randomly selected from each group.

The control group was likewise created from query searches in the New Hampshire's Office of Chief Medical Examiner computer database, using an age range between 20 and 40 years old, whose cause of death was due to cardiac circumstances such as "spontaneous coronary artery dissection," "myocardial infarction due to arteriosclerotic cardiovascular disease," and "mitral valve prolapse" as examples of the many varying cardiac-related causes of death. This group also contains deaths caused by seizure disorders and positional asphyxia. The group is made up of decedents whose death was not obvious upon presentation and therefore could have been thought to be drug-related, but was later determined otherwise. This will allow the study to reveal how accurate the triad predicts deaths to be caused by opiates/opioids when compared against a group of cases that were thought to be potential drug intoxication cases and were later determined otherwise by autopsy and toxicology. While creating the control group, a few decedents were found to have naloxone in their system even though they were not intoxicated from opiates/opioids. This is because in light of the high rates of opiate/opioid intoxications, administration of naloxone has become routine. The control decedents had to be negative for opioids in their postmortem toxicology. With these parameters, 50 age-matched cases between 2010 and 2015 were selected to represent the control group.

Autopsy and toxicology reports for each of the total 150 cases involved in this study were reviewed and analyzed by two pathologists for the presence or absence of pulmonary edema, cerebral edema, and a distended urinary bladder. The pathologists share the same format in which they record autopsy findings. Pulmonary edema was considered present when foamy, proteinaceous fluid was in the trachea, major bronchi, and/or was expressed from the cut surface of the lungs. The pathologists specifically noted whether the decedents had pulmonary edema versus merely congestion in the lungs. Brain weights of each dece-

dent were recorded at autopsy in the fresh state. For this study, these weights were compared to a standard range of organ weights developed by The Ohio State University Department of Pathology (10). For males, this range is 1365 g to 1450 g and for females it is 1250 g and 1275 g. Decedents' brains were also examined for flattening of gyri, narrowing of sulci, and fullness within the cranial cavity for determining the presence or absence of cerebral edema. Histological examination aided in the determination of the presence or absence of both pulmonary edema and cerebral edema in these cases. Decedents in this study were considered to have a distended urinary bladder if it contained 400 mL or more of urine. Previous publication by Rohner et al. had used 350 mL as their minimum distended bladder volume (8). Our study used 400 mL to assure distension and significance for this study in these cases. Bladder evacuation prior to autopsy could not be accounted for and is therefore a limitation to this study.

After reviewing the decedents' information and recording the presence or absence of these findings within each decedent, the data was statistically analyzed.

RESULTS

Pulmonary edema was present in almost all cases of intoxication. It was found in 94% of those who died from opiate/opioid intoxication excluding fentanyl and in 96% of those who died from solely fentanyl intoxication. Cerebral edema, however, was found in 54% of those who died from an opiate/opioid intoxication excluding fentanyl and only in 8% of the study group in which fentanyl was responsible for death. Similarly, urinary bladder distension was found less frequently in the fentanyl study group, arising in only 16% compared to 34% in the study group excluding fentanyl in cause of death. In the control group, pulmonary edema was present in 30%, cerebral edema was present in 2%, and bladder distension had occurred in none. The triad of all three being present simultaneously within a decedent occurred in 8% of those intoxicated and not once in the control group of nonintoxicated decedents (**Table 2**).

Statistical Analysis

The correlation between fatal opiate/opioid drug intoxication and the presence of pulmonary edema, cerebral edema, and urinary bladder distension was carried out using Chi-squared (X^2) test. Results were considered significant at $p<0.05$ (**Table 2**).

Sensitivity, specificity, and positive/negative predictive values were calculated using the data obtained in this study. The sensitivity of pulmonary edema in both study groups was notably higher than the sensitivities of cerebral edema and urinary bladder distension for opiate/opioid-related deaths (94% in the study group excluding fentanyl in cause of death and 96% in the study group of fatal fentanyl intoxications) (**Tables 3 and 4**). The specificity of all three, especially that of cerebral edema and urinary bladder distension, are also very high (**Tables 3 and 4**). In the study group of those who died of opiate/opioid intoxication excluding fentanyl, the positive predictive value of cerebral

edema is 96% and that of urinary bladder distension is 100%. The negative predictive value for the accuracy of absence of pulmonary edema is 92% (**Table 3**).

In the study group of individuals who died of fentanyl intoxication, the specificity for opiate/opioid-related death, when looking at cerebral edema and urinary bladder distension, are both high, but their sensitivity values are small (**Table 4**). Similarly, to the other study group, the positive predictive values for the triad are high, all above 75%. The negative predictive value for pulmonary edema in opiate/opioid-related deaths is 96% (**Table 4**).

DISCUSSION

This study supports a relationship between opiate/opioid intoxication and the presence of pulmonary edema, cerebral edema, and urinary bladder distension due to the much higher frequencies of the three within individuals who died from fatal opiate/opioid intox-

Table 2: Frequencies of Pulmonary Edema, Cerebral Edema, and Urinary Bladder Distension at Autopsy

| Autopsy Findings | Pulmonary Edema | Cerebral Edema | Bladder Distension |
|----------------------------------|-----------------|-----------------|--------------------|
| Study group (excluding fentanyl) | 47/50 (94%) | 27/50 (54%) | 17/50 (34%) |
| Study group (fentanyl only) | 48/50 (96%) | 4/50 (8%) | 8/50 (16%) |
| Control group | 15/50 (30%) | 1/50 (2%) | 0/50 (0%) |
| <i>p</i> -value | <i>p</i> <0.002 | <i>p</i> <0.002 | <i>p</i> <0.002 |

Table 3: Sensitivity, Specificity, Positive and Negative Predictive Values of Study Group Excluding Fentanyl in Cause of Death

| Study Group Excluding Fentanyl in Cause of Death | Pulmonary Edema | Cerebral Edema | Bladder Distension |
|--|-----------------|----------------|--------------------|
| Sensitivity for opiate/opioid-related death | 94% | 54% | 34% |
| Specificity for opiate/opioid-related death | 70% | 98% | 100% |
| Positive predictive value | 76% | 96% | 100% |
| Negative predictive value | 92% | 68% | 60% |

Table 4: Sensitivity, Specificity, Positive and Negative Predictive Values of Study Group of Fentanyl Deaths

| Study Group of Fentanyl Deaths | Pulmonary Edema | Cerebral Edema | Bladder Distension |
|---|-----------------|----------------|--------------------|
| Sensitivity for opiate/opioid-related death | 96% | 8% | 16% |
| Specificity for opiate/opioid-related death | 70% | 98% | 100% |
| Positive predictive value | 76% | 80% | 100% |
| Negative predictive value | 95% | 52% | 54% |

ications than in a control group of cardiac, seizure, and asphyxiation deaths who had negative toxicology reports. Pulmonary edema was found in nearly every case of intoxication regardless of the opiate/opioid involved and therefore, pulmonary edema is extremely predictive to an opiate/opioid overdose. Cerebral edema, however, had interestingly differing results between the two study groups. Cerebral edema was present in over half of those intoxicated from opiates/opioids excluding fentanyl and only in 8% of those who died from intoxication caused solely by fentanyl. Similarly, urinary bladder distension was more frequent in the study group that excluded fentanyl in cause of death than in the fentanyl study group. These differences are likely a reflection of the specific pharmacological effects of fentanyl in comparison to other opioids and opiates. Given its much higher potency, fentanyl and its analogues cause death too rapidly to allow for the accumulation of cerebral edema or urinary bladder distension. All three were still present more commonly in those intoxicated than those in the control group and all three postmortem findings were found simultaneously in individuals in 8% of the combined study groups and never in the control group. Having noted that, the finding of all three within one individual is highly predictive to an opiate/opioid overdose. In our experience, so far, nonopiate/opioid central nervous system depressants such as benzodiazepines and barbiturates seem to lack this rate of reoccurrence of this triad in autopsy.

Unfortunately, bladder evacuation could not be accounted for in this study when obtaining the data. It is information that the pathologists do not receive upon autopsy and certainly limits the study.

Clearly, pulmonary edema alone is not specific to opiate/opioid intoxication. Since this research highlights the relative lack of urinary distension and cerebral edema in fentanyl deaths, reliance on the PMCT triad of pulmonary edema, cerebral edema, and urinary retention to guide toxicological analysis for likely opiate/opioid intoxication would not detect cases of fatal fentanyl intoxication, which has been the leading cause of drug deaths in New Hampshire for the past three years. Previous references use PMCT imaging

to guide similar studies that leads this study to comment on the limitations of virtual autopsy compared to autopsy to fully evaluate drug deaths.

CONCLUSION

Opioid receptor activation has shown to have peripheral and central nervous system effects that, in cases of fatal intoxication, can be seen postmortem via virtual autopsy and traditional autopsy. Pulmonary edema, cerebral edema, and urinary bladder distension have shown to be frequent findings in cases of fatal drug intoxication by the analysis of PMCT scans and autopsy findings. Pulmonary edema is extremely frequent in all cases of fatal opiate/opioid intoxication whereas cerebral edema and urinary bladder distension have shown to be opiate/opioid dependent, arising much less frequently in those who die from solely fentanyl. This is likely because fentanyl, due its substantially increased potency, induces its fatal effects too rapidly to allow the body to accumulate cerebral edema, high urine volumes, and urinary bladder retention. Given these findings, reliance on the triad in PMCT, although not used in this study, would miss cases of fatal fentanyl intoxication, which has become the leading agent of drug deaths in the state of New Hampshire. The simultaneous presence of all three is still highly predictive to an opiate/opioid overdose both in virtual autopsy and autopsy.

REFERENCES

- 1) Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths – United States, 2000-2014. *MMWR Morb Mortal Wkly Rep.* 2016 Jan 1; 64(50-51):1378-82. PMID: 26720857. <https://dx.doi.org/10.15585/mmwr.mm6450a3>.
- 2) Fallon K. Weekly report provided to OCME stakeholders. Concord (NH): New Hampshire Office of the Chief Medical Examiner; 2016 Aug 11. 1 p.
- 3) Algren DA, Monteith CP, Punja M, et al. Fentanyl-associated fatalities among illicit drug users in Wayne County, Michigan (July 2005-May 2006). *J Med Toxicol.* 2013 Mar; 9(1):106-15. PMID: 23359211. PMCID: PMC3576499. <https://dx.doi.org/10.1007/s13181-012-0285-4>.
- 4) Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. *Anesthesiology.* 2011 Dec; 115(6):1363-81. PMID: 22020140. PMCID: PMC3698859. <https://dx.doi.org/10.1097/ALN.0b013e318238bb46>.
- 5) Murray JF. Pulmonary edema: pathophysiology and diagnosis. *Int J Tuberc Lung Dis.* 2011 Feb; 15(2):155-60. PMID: 21219673.

- 6) Jha SK. Cerebral edema and its management. *Med J Armed Forces India*. 2003 Oct; 59(4):326-31.
PMID: 145407555. PMCID: PMC4923559.
[https://dx.doi.org/10.1016/S0377-1237\(03\)80147-8](https://dx.doi.org/10.1016/S0377-1237(03)80147-8).
- 7) Durant PA, Yaksh TL. Drug effects on urinary bladder tone during spinal morphine-induced inhibition of the micturition reflex in unanesthetized rats. *Anesthesiology*. 1988 Mar; 68(3):325-34.
PMID: 3344988. <https://doi.org/10.1097/00000542-198803000-00002>.
- 8) Rohner C, Franckenberg S, Schwendener N, et al. New evidence for old lore – urinary bladder distension on post-mortem computed tomography is related to intoxication. *Forensic Sci Int*. 2013 Feb 10; 225(1-3):48-52. PMID: 22565114.
<https://dx.doi.org/10.1016/j.forsciint.2012.03.029>.
- 9) Winklhofer S, Surer E, Ampanozi G, et al. Post-mortem whole body computed tomography of opioid (heroin and methadone) fatalities: frequent findings and comparison to autopsy. *Eur Radiol*. 2014 Jun; 24(6):1276-82. PMID: 24599624.
<https://dx.doi.org/10.1007/s00330-014-3128-7>.
- 10) Department of Pathology resident's homepage [Internet]. Columbus: Ohio State University, Wexner Medical Center; 2016 [cited 2016 Dec 9]. Available from:
<http://www.pathology.med.ohio-state.edu/residents/autopsy.asp>.

Gabapentin in Mixed Drug Fatalities: Does This Frequent Analyte Deserve More Attention?

Grant Finlayson, Michael Chavarria, Stephanie Chang, Tyler Gardner, Abigail Grande, Colleen MacCallum, Joyce L. deJong, Kelly Quesnelle

ABSTRACT

From 2000 to 2014, drug overdose deaths increased 137% in the United States, and 61% of these deaths included some form of opiate. The vast majority of opiate-related drug fatalities include multiple drugs, although there is scant data quantitatively describing the exact drugs that contribute to deaths due to multiple drugs. In the present study, we sought to quantitatively identify the drugs that occur with opiates in accidental multidrug-related fatalities. We retrospectively explored fatal drug trends in four Michigan counties, with a focus on profiling drugs present concurrently with opiates. Blood and urine toxicology reports for mixed drug fatalities (N=180) were analyzed using frequent item analysis approaches to identify common analyte trends in opiate-related fatalities. Within our cohort, the most prevalent serum analytes included caffeine (n=147), morphine (n=90), alprazolam (n=69), gabapentin (n=46), and tetrahydrocannabinol (n=44). In 100% of cases where gabapentin was present (n=46), an opiate was also present in the serum or urine. The average gabapentin serum concentration was 13.56 µg/mL (SEM =0.33 µg/mL), with a range of 0.5-88.7 µg/mL. Gabapentin was found at very high frequency in accidental mixed drug fatalities. Gabapentin concentrations were generally within the normal therapeutic range (2-20 µg/mL). It is unknown whether a synergistic effect with opioids may contribute to central respiratory depression. Further research is warranted to determine any contributory role of gabapentin in these deaths. Confirmed interactions could have broad implications for future reporting by forensic pathologists as well as prescribing practices by clinicians. *Acad Forensic Pathol.* 2017 7(1): 99-111

AUTHORS

Grant Finlayson BS, Western Michigan University Homer Stryker MD School of Medicine - Biomedical Science/Pathology

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

Michael Chavarria BA, Western Michigan University Homer Stryker MD School of Medicine - Biomedical Science

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

Stephanie Chang BA, Western Michigan University Homer Stryker MD School of Medicine - Biomedical Science

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

Tyler Gardner BS, Western Michigan University Homer Stryker MD School of Medicine - Biomedical Science

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

Abigail Grande MPH, Western Michigan University Homer Stryker MD School of Medicine - Pathology

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

Colleen MacCallum MS, Western Michigan University Homer Stryker MD School of Medicine - Epidemiology and Biostatistics

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

Joyce L. deJong DO, Western Michigan University Homer Stryker MD School of Medicine - Pathology

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

Kelly Quesnelle PhD, Western Michigan University Homer Stryker MD School of Medicine - Biomedical Science

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

CORRESPONDENCE

Kelly Quesnelle PhD, 1000 Oakland Dr Kalamazoo MI 49008-1202, kelly.quesnelle@med.wmich.edu

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects



STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

This work was presented at the 2016 NAME Annual Meeting. The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Gabapentin, Opioid overdose, Hydrocodone, Substance abuse, Mixed-drug fatality

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.012>

Submitted for consideration on 10 Oct 2016. Accepted for publication on 29 Nov 2016

INTRODUCTION

The opiate abuse epidemic in the United States is a growing health crisis that shows little evidence of subsiding in the near future. Opioid substances now account for more than half of all accidental overdose deaths (1). From 1999 to 2014, opioid overdose deaths rose by almost four-fold, closely mirroring an approximate four-fold increase in the sales of prescription opioids. Importantly, this rise in opioid use did not affect reports of subjective levels of pain (2, 3). Nearly half a million people have died during this time frame as a result of opioid abuse (1).

There have been a plethora of studies confirming this opioid use phenomenon, specifically in the postmortem toxicology analysis of accidental drug-related fatalities. Often, these drug-related fatalities include multiple pharmacologic agents in addition to opiates. However, while data on opiate-related fatalities are abundant, there is a paucity of data describing the nonopiate substances found concurrently with opioids in multidrug fatalities. By determining what substances are present with opioids, we can better appreciate the toxicological context in which these deaths are occurring.

The primary mechanism of death in an opioid-induced overdose is central respiratory depression. It is well known that other central nervous system depressants, including ethanol and benzodiazepines, can act synergistically with opioids to exacerbate respiratory depression, resulting in hypoxia and eventual death (4). There is less clarity regarding how other nonopiates may interact with opiates. In addition to exacerbating respiratory depression through synergistic central nervous system depression, nonopiates may have pharmacokinetic interactions with opiates. Such interactions could increase the concentration of opiate in the blood, increasing the likelihood of undesired or fatal effects. The extent to which combined perimortem blood concentrations of opioids and other substances contribute to death has not been well-described. In the present study, we sought to identify potential pairings between opiates and nonopiates that may contribute to death.

METHODS

Study Subjects

Deceased adults (greater than or equal to 18 years of age) that met inclusion criteria for cause of death, manner of death, and county of death were identified from the death investigation database currently used by the Office of the Medical Examiner in southwest Michigan. Study subjects were deceased in Allegan, Calhoun, Kalamazoo, or Muskegon counties in Michigan from January 1, 2013 to December 31, 2015. The cause of death for all study subjects was classified as “drug-related” and the manner of death was determined to be “accident.” All study subjects had a toxicology report on file within the database. Additional demographic information was obtained for each study subject, including age, sex, and race (**Table 1**).

Analyte Prevalence

Each toxicology report was de-identified and reviewed by at least two individuals. Analytes data were recorded and automatically converted to a binary database to generate “present” or “not present” calls for

Table 1: Demographic Data on Study Subjects

| All Decedents | N = 180 (100%) |
|----------------------------|----------------|
| Age (Years) | |
| Mean | 42 |
| Range | 18-81 |
| Age Category (Years) | |
| 18-35 | 57 (31.6) |
| 36-65 | 116 (64.4) |
| 66+ | 7 (3.8) |
| Sex | |
| Male | 113 (62.8) |
| Female | 67 (37.2) |
| Race | |
| White | 148 (82.2) |
| Hispanic | 5 (2.8) |
| Black or African American | 26 (14.4) |
| American Indian or Alaskan | 1 (0.6) |

each analyte across all the cases. Prevalence values are the frequency of occurrence for each analyte within the toxicology report subtype (n=180 for blood and urine combined, n=178 for blood reports, and n=144 for urine reports). A prevalence of 1.0 would indicate that the analyte is present in every case.

Descriptive Analysis: Frequent Item Analysis

Frequent item analysis (FIA) is used to identify common combinations (subset or whole) within a “transaction” (5). For example, consider the following four transactions at a grocery store:

Transaction #1: milk, bread, butter, spaghetti noodles, pasta sauce

Transaction #2: eggs, spaghetti noodles, pasta sauce, bananas, apples

Transaction #3: garlic bread, spaghetti noodles, pasta sauce

Transaction #4: spaghetti noodles, eggs

All four transactions have a unique combination of items purchased, but three out of the four have a common subset combination of spaghetti noodles and pasta sauce. Frequent item analysis is used to identify these common combinations within multiple transactions. In this case, our “transaction” is an overdose case, and our “items” are drug analytes. In frequent item analysis, there are two parameters of interest for which the investigator sets: support and confidence. Support is the proportion of cases in which the combination of items ($X|Y$) is found. Confidence is the conditional probability in which item Y was present given that item X was present. For instance, going back to our grocery transaction example, we had a support of 0.75 and a confidence of 1.00 for the combination of (pasta sauce | spaghetti noodles), indicating 75% of transactions included pasta sauce and spaghetti noodles, and that 100% of transactions with pasta sauce also included spaghetti noodles. These parameters are set by the investigator, and for the analyses presented herein, support=0.2 and confidence=0.7. The FIAs presented here use a candidate-based approach in which only the cases with the candidate of interest are included in each respective analysis, allowing for

combinations with that candidate to be explored. In this analysis we were primarily interested with support given that the candidate was always part of the combination, resulting in a confidence of 1.0. It is important to note that FIA is a purely descriptive analysis, and as a descriptive analysis, there is no *p*-value or confidence level associated with the FIA analysis.

Inferential Statistical Analysis

Blood gabapentin concentrations were compared in those cases involving hydrocodone versus those cases that did not involve hydrocodone using a two-tailed heteroscedastic *t*-test. For concentration correlations between gabapentin and hydrocodone, concentrations were plotted on two-dimensional axes and a linear regression with Pearson’s correlation coefficient was determined.

RESULTS

Prevalence of Analytes

The first analysis performed was a simple frequency analysis to identify the most common analytes present in blood toxicology reports, urine toxicology reports, or both. Of these N=180 cases, we had both a urine and blood sample for n=143 cases. We had a blood sample for n=178 cases and a urine sample for n=144 cases. The number of analytes detected in the blood and urinalysis of each individual ranged from 0-18, with an average of 7.44 ± 3.05 analytes per individual. One individual had no analytes present in either the blood or the urine toxicology reports but was included in the analysis because the death was ruled an accidental multidrug-related fatality. The single most common analyte detected was caffeine, occurring with a relative frequency of 82% (n=148) in the combined blood and urinalysis reports. Because this common analyte was so prevalent and generally does not contribute to death, we excluded this analyte from further analysis in this study.

Opiate analytes were present in 90.6% of all cases. The frequency of opiate analytes across the blood and urine analyses combined occurred as follows: mor-

phine (55%), monoacetylmorphine (34%), codeine (28%), hydromorphone (26%), methadone (23%), and fentanyl (21%) (**Figure 1**). Less frequent opiates include hydrocodone (18%), oxycodone (11%), and oxymorphone (9%). All other opiates were found at frequencies less than 5%. Heroin is infrequently detectable in the blood because it rapidly undergoes deacetylation into 6-monoacetylmorphine, which can be detected in the blood and urine and is used as a specific and proven biomarker for heroin (6, 7). Opioids can present differently in the blood and urine because they are generally converted into polar metabolites eliminated in the urine, and urine volume can vary widely. This change in volume influences urine

analyte concentration and renders it generally less reliable than blood analysis. To that end, we also report analyte frequency in the blood and urine separately. The frequency of opiates in the urine occurred as follows: morphine (51%), monoacetylmorphine (32%), hydromorphone (31%), codeine (27%), methadone (24%), fentanyl (21%), and hydrocodone (20%) (**Figure 2**). The frequency of opiates in the blood occurred as follows: morphine (51%), methadone (22%), and monoacetylmorphine (20%) (**Figure 3**).

The analyte concentrations of all nonopiates in the blood and urine were also examined. A combined analysis of blood and urine nonopiates revealed an-

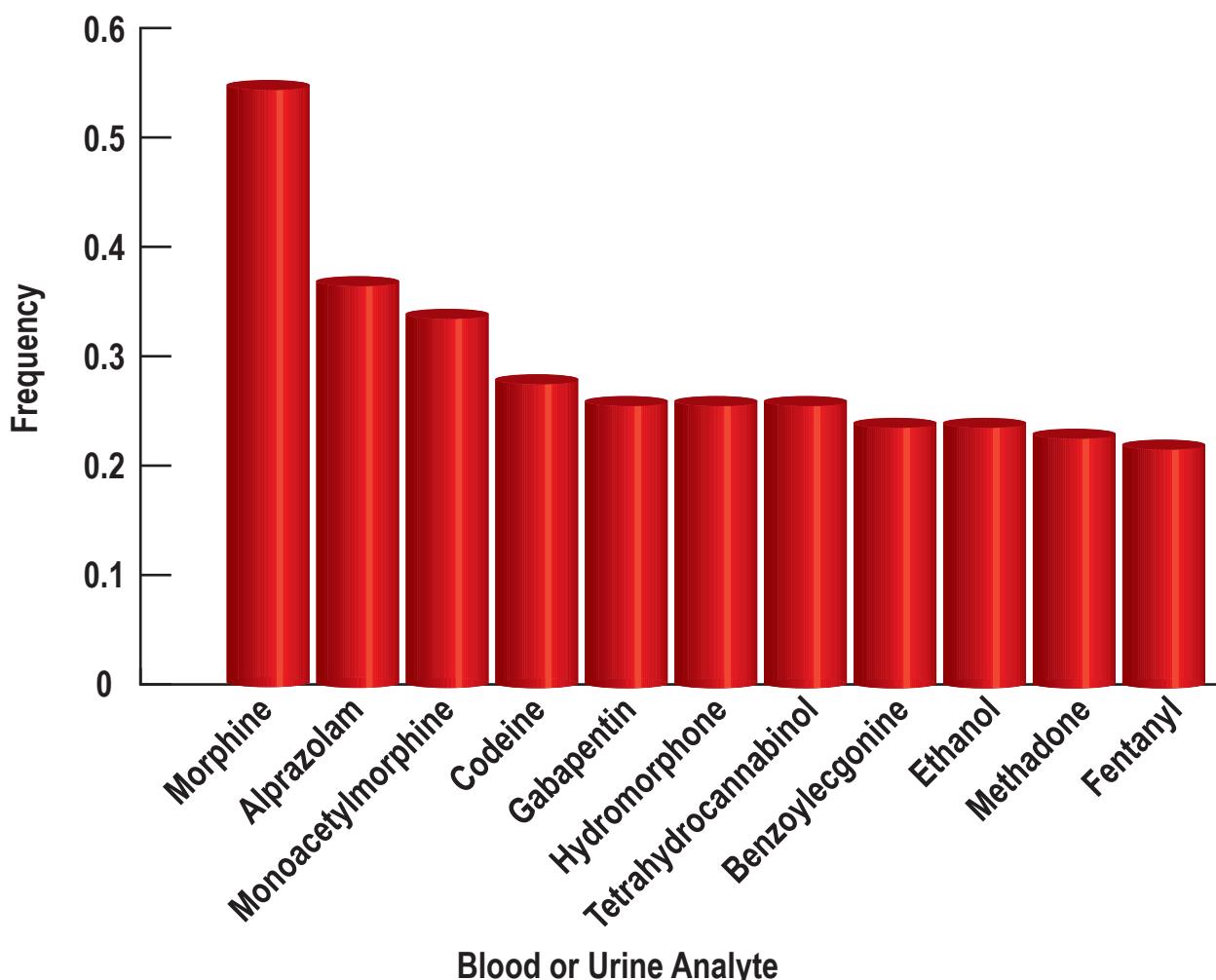


Figure 1: The most common analytes when considering both blood and urine toxicology of N=180 subjects that occur with a frequency >0.2.

alyte prevalence of 20% or greater as follows: alprazolam (36%), gabapentin (26%), tetrahydrocannabinol (THC, 26%), benzoylecgonine (24%), and ethanol (24%) (**Figure 1**). Alprazolam is a commonly prescribed benzodiazepine manufactured most commonly under the trade name Xanax. Cocaine is metabolized into benzoylecgonine, which can be detected in the urine. The prevalence levels of all nonopiates in the urine for which the prevalence was 20% or greater occurred as follows: alprazolam (28%), benzoylecgonine (27%), and ethanol (22%) (**Figure 2**). All of the cases in which urinalysis was positive for alprazolam also tested positive for alpha-hydroxy-alpra-

zolam. The prevalence levels of all nonopiates in the blood (for which the prevalence was 20% or greater) occurred as follows: alprazolam (36%), gabapentin (26%), THC (25%), and ethanol (22%) (**Figure 3**).

Frequent Item Associations

We initially performed an unbiased frequent item association (support ≥ 0.20 , confidence ≥ 0.7) to identify multidrug combinations of frequently occurring analytes. This analysis yielded only combinations of common opiates (data not shown), and did not provide any additional information regarding associa-

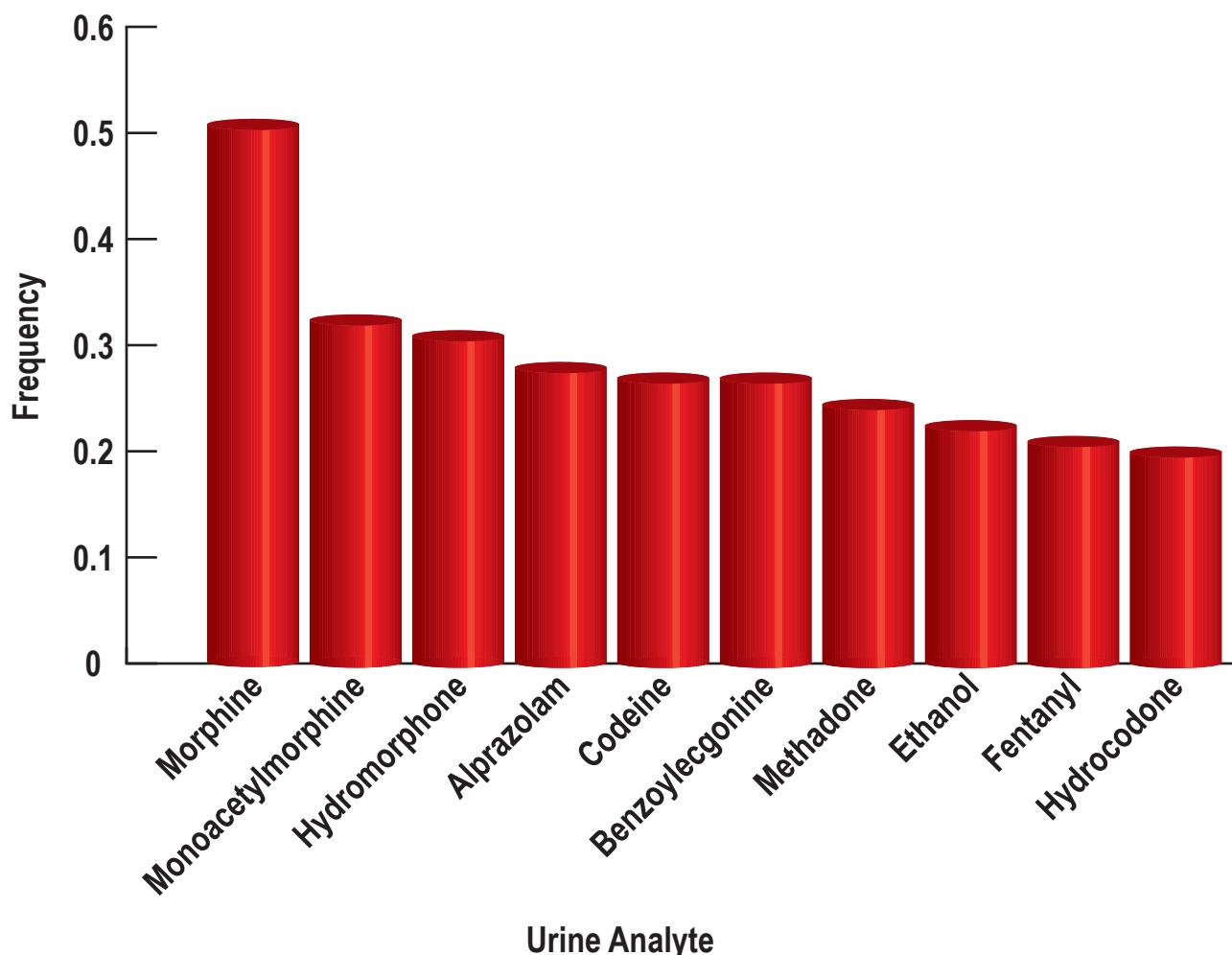


Figure 2: The most common analytes from the urine samples of n=144 subjects for whom urinalysis was available that occur with a frequency >0.2 .

tions with nonopiate analytes. To assess the potential contribution of nonopiates to the seemingly opiate-mediated mortality, we identified the most common combinations that included frequent nonopiate analytes. Frequent nonopiate analytes were defined as nonopiate analytes that appeared in the combined blood and urine analyses at a relative frequency of 20% or greater. This included alprazolam, benzoylecgonine, ethanol, gabapentin, and THC. For each of these analytes, a data subset was created to include information for only cases that involved the candidate analyte. Frequent item analysis was then employed using a support of 0.2 and a confidence of 0.7 for each candidate.

Frequent item analysis revealed that many of the most common opiate analytes are present in a similar proportion across the cases containing each of the candidate nonopiates we examined (**Table 2**). For example, morphine occurred with a relative frequency of 0.52 in the alprazolam-containing cases. (This means that 52% of all cases containing alprazolam also contained morphine). Likewise, morphine was present with a relative frequency of 0.66, 0.57, 0.57, and 0.62 in cases containing benzoylecgonine, ethanol, gabapentin, and THC, respectively. None of these relative frequencies are especially remarkable considering that morphine was present with a relative frequency of 0.55 across all cases.

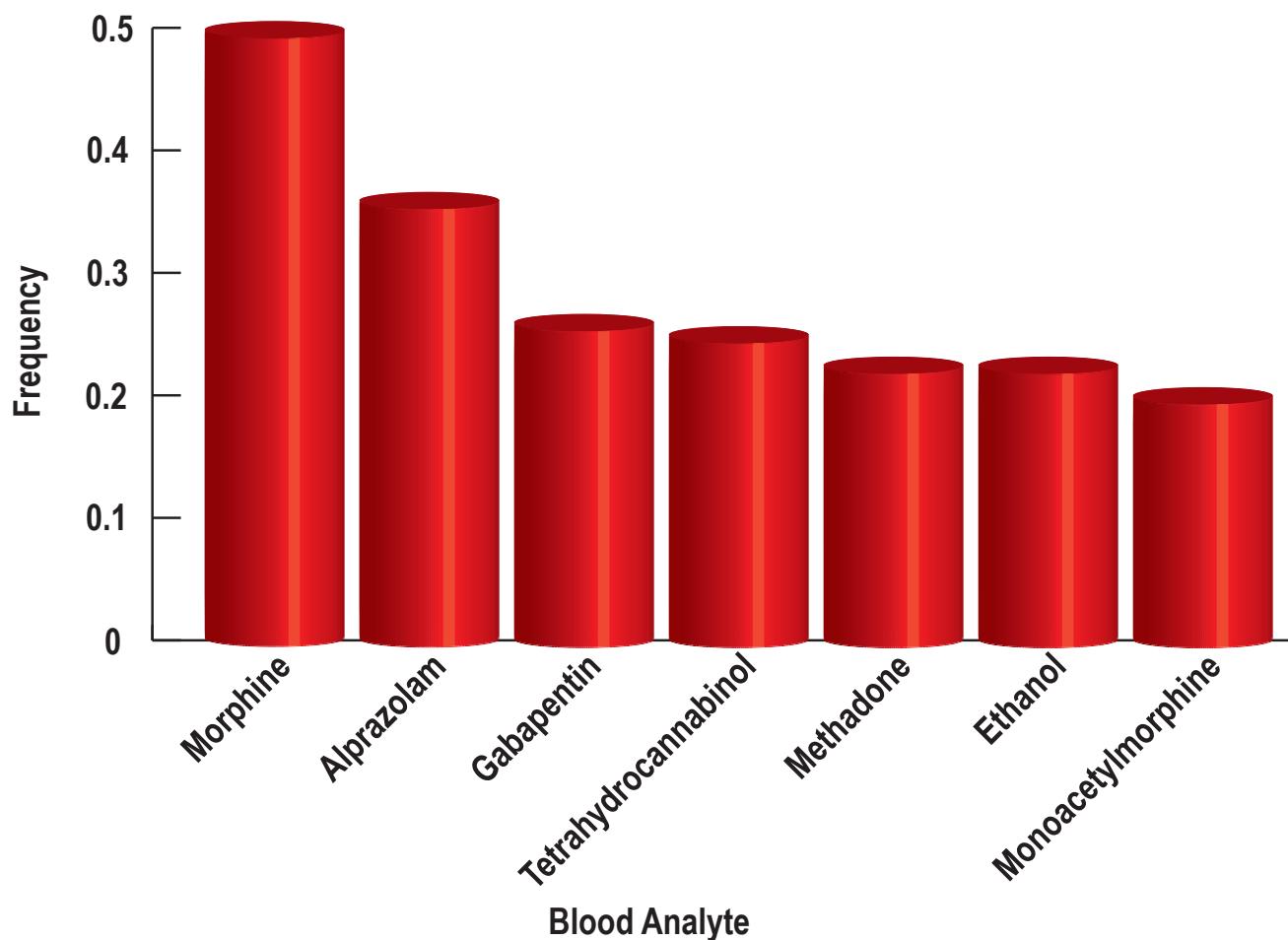


Figure 3: The most common analytes from the blood samples of n=178 subjects for whom blood toxicology was available that occur with a frequency >0.2.

More remarkable, however, is the case of hydrocodone. Hydrocodone was present at a relative frequency of 0.18 across all cases. However, in gabapentin-containing cases, hydrocodone was present with a relative frequency of 0.26. In addition, the hydrocodone-containing drug combination of hydrocodone and hydromorphone was present at a frequency of 0.22 in the cases with gabapentin (**Table 2**). In contrast, hydrocodone and hydrocodone-containing drug combinations were present at a frequency of ≤ 0.2 in cases containing alprazolam, benzoylecgonine, ethanol, and THC. Thus, hydrocodone is observed to be present more frequently in cases with gabapentin toxicity than across the regular population of mixed drug fatalities, although these are not mutually exclusive

groups so a chi-square test cannot be used to determine the significance of this observation.

Gabapentin and Hydrocodone Concentrations

Because it is reported that hydrocodone and gabapentin have a pharmacokinetic interaction whereby hydrocodone increases gabapentin drug exposure (8), we next sought to determine whether gabapentin concentrations in the blood are increased to supratherapeutic concentrations in decedents who also tested positive for hydrocodone. To assess this, we examined the blood concentrations of gabapentin in decedents who concurrently tested positive for hydrocodone against the blood concentrations of gabapentin in decedents

Table 2: Frequent Item Analysis of Opiate Associations with Each Nonopiate Examined Using a Candidate-Based Approach

| | Alprazolam | Benzoylecgonine | Ethanol | Gabapentin | Tetrahydrocannabinol |
|---------------------------------------|------------|-----------------|---------|------------|----------------------|
| Alprazolam | 1.00 | 0.32 | 0.20 | 0.35 | 0.43 |
| Aminoclonazepam | 0.20 | <0.20 | <0.20 | 0.22 | 0.30 |
| Benzoylecgonine | 0.22 | 1.00 | 0.23 | <0.20 | <0.20 |
| Codeine | 0.25 | 0.41 | 0.23 | 0.30 | 0.32 |
| Ethanol | <0.20 | 0.23 | 1.00 | 0.22 | 0.26 |
| Fentanyl | 0.20 | 0.20 | 0.20 | <0.20 | 0.22 |
| Gabapentin | 0.25 | <0.20 | 0.23 | 1.00 | <0.20 |
| Hydrocodone | <0.20 | <0.20 | 0.20 | 0.26 | <0.20 |
| Hydromorphone | 0.26 | 0.32 | 0.20 | 0.30 | 0.23 |
| Methadone | 0.29 | 0.25 | <0.20 | 0.22 | <0.20 |
| Monoacetylmorphine | 0.28 | 0.50 | 0.45 | 0.33 | 0.36 |
| Morphine | 0.52 | 0.66 | 0.57 | 0.57 | 0.62 |
| Tetrahydrocannabinol | 0.31 | 0.20 | 0.27 | <0.20 | 1.00 |
| Alprazolam, morphine | <0.20 | <0.20 | <0.20 | <0.20 | 0.21 |
| Codeine, monoacetylmorphine | 0.23 | 0.41 | 0.20 | 0.26 | 0.26 |
| Codeine, morphine | 0.25 | 0.41 | 0.20 | 0.30 | 0.30 |
| Hydrocodone, hydromorphone | <0.20 | <0.20 | <0.20 | 0.22 | <0.20 |
| Hydromorphone, morphine | <0.20 | 0.20 | <0.20 | <0.20 | <0.20 |
| Monoacetylmorphine, morphine | 0.28 | 0.50 | 0.45 | 0.33 | 0.36 |
| Codeine, monoacetylmorphine, morphine | 0.23 | 0.41 | 0.20 | 0.26 | 0.26 |

Support values are given. Row indicates A and column indicates B in the conditional (A|B). All combinations where support ≥ 0.2 are shown. Hydrocodone and hydrocodone-containing multidrug combinations occur more frequently with gabapentin than the other nonopiates we examined.

who did not test positive for hydrocodone (**Figure 4**). The average blood gabapentin concentration in decedents with positive hydrocodone toxicology ($n=12$) was $11.98 \pm 2.52 \mu\text{g/mL}$. The range of blood gabapentin concentrations in this population was from $11 \mu\text{g/mL}$ to $172 \mu\text{g/mL}$. Meanwhile, the average blood concentration of gabapentin in decedents with negative hydrocodone toxicology ($n=34$) was $14.11 \pm 2.92 \mu\text{g/mL}$. The range of blood gabapentin concentrations in these decedents ranged from $0.9 \mu\text{g/mL}$ to $27.5 \mu\text{g/mL}$. Gabapentin is generally considered therapeutic at concentrations $<20 \mu\text{g/mL}$, although concentrations

are often <10 µg/mL (9, 10). Overall, the gabapentin concentrations between these two groups were not statistically different ($p=0.592$), and the means were below 20 µg/mL, suggesting that the presence of hydrocodone does not cause gabapentin to be increased to supratherapeutic concentrations in these patients.

It has been reported that gabapentin increases hydrocodone elimination (8), so we next investigated whether gabapentin decreased the blood concentrations of hydrocodone. Blood hydrocodone concentrations in decedents who tested positive for both gabapentin

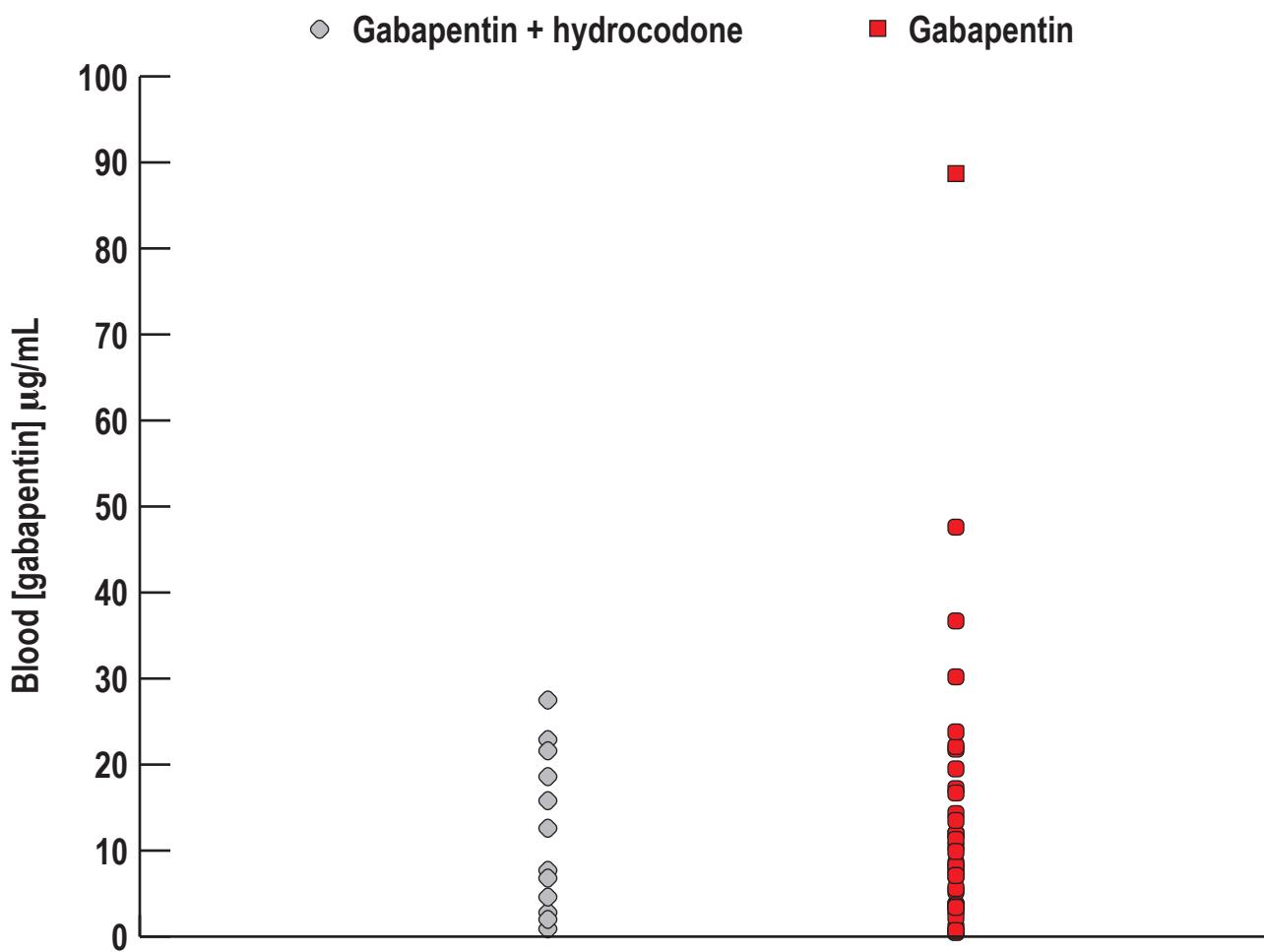


Figure 4: Gabapentin concentration in the presence or absence of hydrocodone. The average blood gabapentin concentration in decedents with positive hydrocodone toxicology ($n=12$) was $11.98 \mu\text{g/mL} \pm 2.52$. The average blood concentration of gabapentin in decedents with negative hydrocodone toxicology ($n=34$) was $14.11 \mu\text{g/mL} \pm 2.92$.

and hydrocodone ranged from 0 µg/mL to 514 µg/mL, with the average blood hydrocodone concentration being 99.03 ± 40.93 µg/mL (**Figure 5**). Hydrocodone detection was negative in two blood samples for which the corresponding decedent urine specimens tested positive. In these two cases, the urine hydrocodone concentrations were 192 µg/mL and 875 µg/mL, with corresponding blood gabapentin concentrations of 4.6 µg/mL and 15.8 µg/mL, respectively.

There appears to be no significant direct or inverse association between concentrations of blood hydrocodone and blood gabapentin (Pearson correlation coefficient = 0.0051).

Although there seemed to be no correlation in blood gabapentin with decreasing blood hydrocodone concentrations, we investigated the relationship between

blood gabapentin and urine hydrocodone concentration to detect whether urine hydrocodone concentrations may be higher in cases with positive gabapentin toxicology. The urine hydrocodone concentrations in decedents who tested positive for both gabapentin and hydrocodone ranged from 192 ng/mL to 10 000 ng/mL, with an average urine hydrocodone concentration of $3365.50 \text{ ng/mL} \pm 873$ (**Figure 6**). When values of urine hydrocodone are plotted with respect to blood gabapentin concentrations, there does not seem to be a direct or inverse correlation between the two concentrations (Pearson correlation coefficient = 0.2812).

DISCUSSION

Gabapentin, or 1-(aminomethyl)cyclohexaneacetic acid, was first approved for use in the United States in 1993. It is widely prescribed as a treatment for seizure disor-

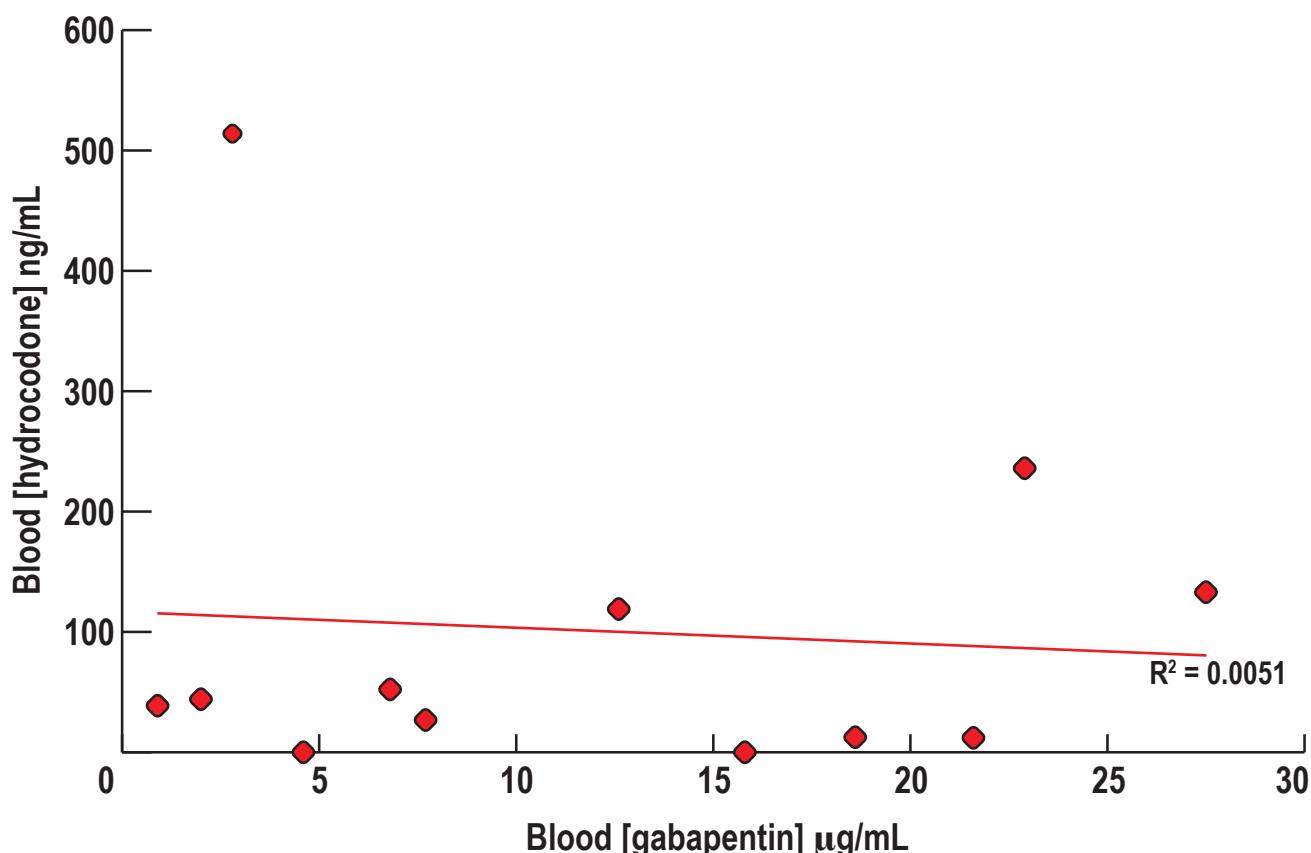


Figure 5: Hydrocodone concentration in the blood versus gabapentin concentration. There appears to be no significant direct or inverse association between concentrations of blood hydrocodone and blood gabapentin ($R^2 = 0.0051$).

ders and neuropathic pain syndromes, including postherpetic neuralgia and diabetic neuropathy. Additionally, it is prescribed for off-label use in managing conditions such as restless legs syndrome and anxiety disorders (11, 12). Prescribed dosages of gabapentin vary with the condition it is intended to treat, but generally fall between 300-3600 mg per day (13). The effective therapeutic concentration in blood is 2-20 µg/mL, with concentrations greater than 25 µg/mL noted as being toxic (9, 10). The recorded side effects of people experiencing a gabapentin overdose include dizziness, drowsiness, ataxia, nausea, tremor, and increased risk of suicide (8, 14).

Gabapentin binds to the $\alpha_2\delta$ subunit of N-type voltage-gated calcium ion channels (15) and modulates synthesis of both GABA and glutamate through interactions with glutamate decarboxylase and branched chain aminotransferase (16). While many sites of ga-

bapentin binding such as these have been identified, the precise mechanism by which gabapentin-mediated modulation of calcium channels may influence neuropathic pain remains unknown. The co-occurrence of gabapentin with opioid metabolites in our study begs the question of whether gabapentin had any contributory effect to the mechanism of death in the subjects. Opioids have been shown to close N-type voltage-gated calcium channels through indirect OP_2 -receptor interactions, thereby causing decreased neuronal excitability through hyperpolarization (17). Since this $\alpha_2\delta$ subunit of N-type channels is also the target of gabapentin inhibition, it stands to reason that the co-occurrence of gabapentin and opioids in the body could affect the function of these N-type channels in unintended ways. Opioids with a higher affinity for the OP_2 receptor could possibly have a more pronounced interaction through this mechanism.

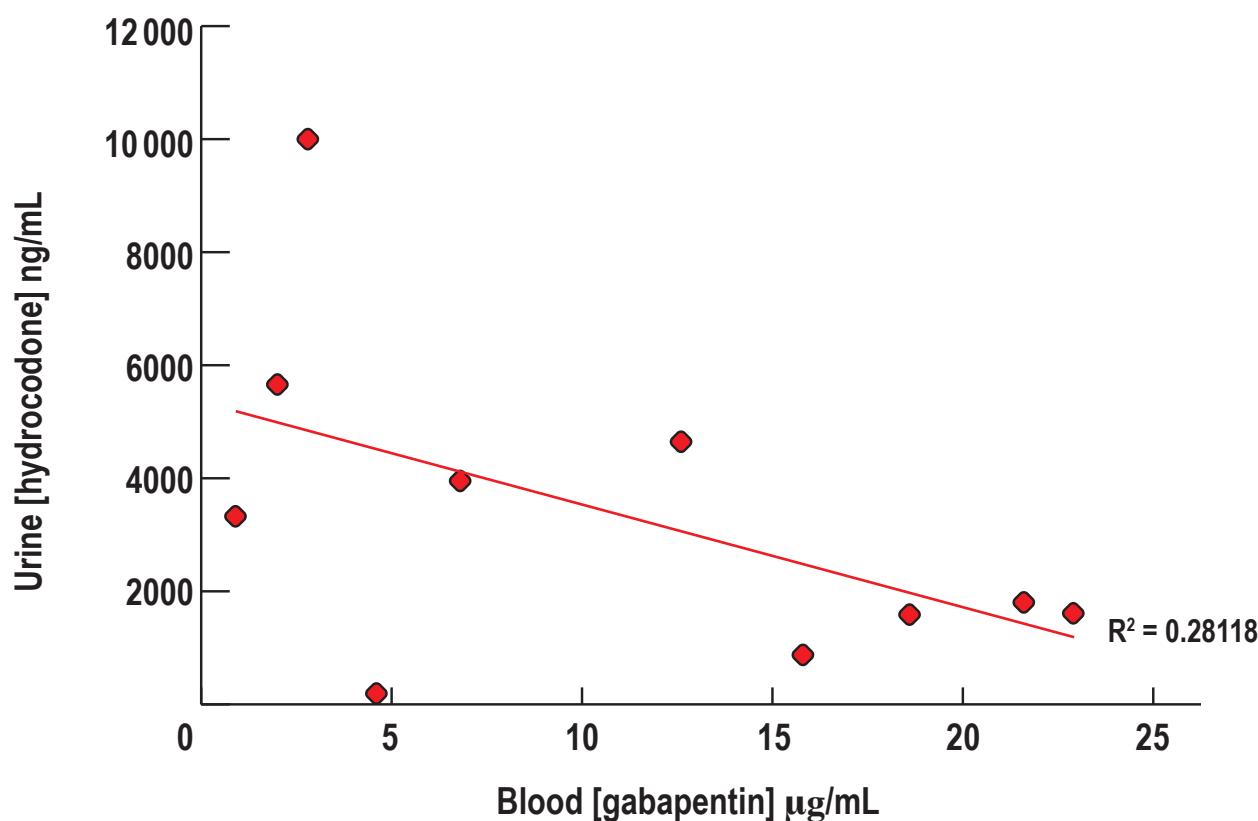


Figure 6: Hydrocodone concentration in the urine versus gabapentin concentration. There appears to be no significant direct or inverse association between concentrations of urine hydrocodone and blood gabapentin ($R^2 = 0.28118$).

In our study, gabapentin was most frequently found to be associated with hydrocodone as a co-occurring metabolite. It has been documented that the presence of gabapentin decreases hydrocodone exposure in a dose-dependent manner. Conversely, hydrocodone has been reported to increase the drug exposure of gabapentin by 14% (8). In our study, however, the presence or absence of hydrocodone did not correlate with differences in the average concentration of gabapentin. It has also been reported that co-administration of gabapentin and other opiates such as morphine may alter the pharmacokinetic profile of gabapentin. We did not focus on that work here, as the drug exposure of the opiate is unchanged in these cases, (8) and we did not identify an increased association between gabapentin and any other opiate besides hydrocodone.

Perhaps one of the more intriguing aspects of gabapentin in our study is the significant co-occurrence of gabapentin with other metabolites of drugs prone to abuse. This discovery prompted the exploration of the manner in which gabapentin is used, whether as prescribed or as a potential drug of abuse. A previous study of prison inmates showed that of the population sampled who had an opiate use disorder, 26% reported intentional abuse of gabapentin (18). The reasons for gabapentin abuse remain unclear, although reports suggest that gabapentin may help relieve symptoms of opioid withdrawal (19), potentially contributing to the high co-occurrence with opioids in our study.

Interestingly, a 2010 report from the Scottish Drug and Crime Enforcement Agency illustrated an appreciable amount of gabapentin retrieved from prisons and on the street, largely in the form as a cutting agent with heroin (20). On a molecular level, gabapentin would appear to be an appropriate cutting agent. Both are odorless white crystalline solids, and the melting temperature of gabapentin (162–166°C) is similar to that of diacetylmorphine (172°C). This is noteworthy as the process of injecting heroin involves melting the substance in preparation for injection. Subjectively, the effects of gabapentin would complement or augment those of diacetylmorphine, making it potentially less likely for the user to notice the adulterant.

CONCLUSION

While the significant occurrence of gabapentin deserves acknowledgement, our data does not definitively suggest that gabapentin was a causative or contributory factor in the deaths of our sample population. With the exception of minimal outliers, the gabapentin concentration of the vast majority of our sample population was well within the therapeutic range, preventing suspicion that gabapentin toxicity alone played a role in the deaths. Numerous drug interactions have been identified and/or suspected with gabapentin, but because the exact mechanism has not been elucidated, definitive conclusions regarding its contribution to overdose deaths cannot be made. Further research exploring these interactions would allow for more complete understanding of the mechanisms of gabapentin. Verified interactions that produce undesirable effects could significantly change prescribing practices of gabapentin, especially if they are more likely to contribute to accidental death.

REFERENCES

- 1) Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths—United States, 2000–2014. *MMWR Morb Mortal Wkly Rep.* 2016 Jan 1; 64(50–51):1378–82. PMID: 26720857. <https://dx.doi.org/10.15585/mmwr.mm6450a3>.
- 2) Chang HY, Daubresse M, Kruszewski SP, Alexander GC. Prevalence and treatment of pain in EDs in the United States, 2000 to 2010. *Am J Emerg Med.* 2014 May; 32(5):421–31. PMID: 24560834. <https://dx.doi.org/10.1016/j.ajem.2014.01.015>.
- 3) Daubresse M, Chang HY, Yu Y, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000–2010. *Med Care.* 2013 Oct; 51(10):870–8. PMID: 24025657. PMCID: PMC3845222. <https://dx.doi.org/10.1097/MLR.0b013e3182a95d86>.
- 4) White JM, Irvine RJ. Mechanisms of fatal opioid overdose. *Addiction.* 1999 Jul; 94(7):961–72. PMID: 10707430. <https://doi.org/10.1046/j.1360-0443.1999.9479612.x>.
- 5) Hahsler M, Grün B, Hornik K, Buchta C. Introduction to arules – a computational environment for mining association rules and frequent item sets. *J Stat Softw [Internet].* 2005 [cited 2016 Oct 10]; 14(15):1–25. Available from: <https://cran.r-project.org/web/packages/arules/vignettes/arules.pdf>.
- 6) Paul BD, Mitchell JM, Mell LD Jr, Irving J. Gas chromatography/electron impact mass fragmentometric determination of urinary 6-acetylmorphine, a metabolite of heroin. *J Anal Toxicol.* 1989 Jan–Feb; 13(1):2–7. PMID: 2709823. <https://doi.org/10.1093/jat/13.1.2>.
- 7) Kolbrich EA, Barnes AJ, Gorelick DA, et al. Major and minor metabolites of cocaine in human plasma following controlled subcutaneous cocaine administration. *J Anal Toxicol.* 2006 Oct; 30(8):501–10. PMID: 17132243. <https://doi.org/10.1093/jat/30.8.501>.

- 8) Food and Drug Administration [Internet]. Washington: U.S. Food and Drug Administration; c2011. Neurontin (gabapentin) capsules; [cited 2016 Oct 10]. 34 p. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020235s036.020882s022,021129s022lbl.pdf.
- 9) Cantrell FL, Mena O, Gary RD, McIntyre IM. An acute gabapentin fatality: a case report with postmortem concentrations. *Int J Legal Med.* 2015 Jul; 129(4):771-5. PMID: 25904080. <https://dx.doi.org/10.1007/s00414-015-1193-3>.
- 10) Tjandrawinata RR, Setiawati E, Putri RS, et al. Single dose pharmacokinetic equivalence study of two gabapentin preparations in healthy subjects. *Drug Des Devel Ther.* 2014 Sep 4; 8:1249-55. PMID: 25214768. PMCID: PMC4159312. <https://dx.doi.org/10.2147/DDT.S69326>.
- 11) Mack A. Examination of the evidence for off-label use of gabapentin. *J Manag Care Pharm.* 2003 Nov-Dec; 9(6):559-68. PMID: 14664664. <https://dx.doi.org/10.18553/jmcp.2003.9.6.559>.
- 12) Mula M, Pini S, Cassano GB. The role of anticonvulsant drugs in anxiety disorders: a critical review of the evidence. *J Clin Psychopharmacol.* 2007 Jun; 27(3):263-72. PMID: 17502773. <https://dx.doi.org/10.1097/jcp.0b013e318059361a>.
- 13) Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. *Clin Ther.* 2003 Jan; 25(1):81-104. PMID: 12637113. [https://doi.org/10.1016/s0149-2918\(03\)90011-7](https://doi.org/10.1016/s0149-2918(03)90011-7).
- 14) Middleton O. Suicide by gabapentin overdose. *J Forensic Sci.* 2011 Sep; 56(5):1373-5. PMID: 21554310. <https://dx.doi.org/10.1111/j.1556-4029.2011.01798.x>.
- 15) Hendrich J, Van Minh AT, Heblisch F, et al. Pharmacological disruption of calcium channel trafficking by the alpha₂delta ligand gabapentin. *Proc Natl Acad Sci U S A.* 2008 Mar 4; 105(9):3628-33. PMID: 18299583. PMCID: PMC2265195. <https://dx.doi.org/10.1073/pnas.0708930105>.
- 16) Taylor CP, Gee NS, Su TZ, et al. A summary of mechanistic hypotheses of gabapentin pharmacology. *Epilepsy Res.* 1998 Feb; 29(3):233-49. PMID: 9551785. [https://doi.org/10.1016/s0920-1211\(97\)00084-3](https://doi.org/10.1016/s0920-1211(97)00084-3).
- 17) Tallent M, Dichter MA, Bell GI, Reisine T. The cloned kappa opioid receptor couples to an N-type calcium current in undifferentiated PC-12 cells. *Neuroscience.* 1994 Dec; 63(4):1033-40. PMID: 7700508. [https://doi.org/10.1016/0306-4522\(94\)90570-3](https://doi.org/10.1016/0306-4522(94)90570-3).
- 18) Bastiaens L, Galus J, Mazur C. Abuse of gabapentin is associated with opioid addiction. *Psychiatr Q.* 2016 Dec; 87(4):763-7. PMID: 26887855. <https://dx.doi.org/10.1007/s11126-016-9421-7>.
- 19) Stoica N, Russell D, Weidner G, et al. Opioid-induced hyperalgesia in chronic pain patients and the mitigating effects of gabapentin. *Front Pharmacol.* 2015 May 27; 6:104. PMID: 26074817. PMCID: PMC4444749. <https://dx.doi.org/10.3389/fphar.2015.00104>.
- 20) Smith BH, Higgins C, Baldacchino A, et al. Substance misuse of gabapentin. *Br J Gen Pract.* 2012 Aug; 62(601):406-7. PMID: 22867659. PMCID: PMC3404313. <https://dx.doi.org/10.3399/bjgp12X653516>.



Primary Cardiac Tumors in Infancy: A Case Report and Literature Review

Carolina Dominguez, Ashley Perkins, Alexandra Duque, Viagnney Bravo

ABSTRACT

Sudden death in infants due to primary cardiac tumors is extremely rare. Herein we describe a case of an 8-month-old male infant, without any previous medical history, who died in a hospital in the city of Medellín-Antioquia, Colombia. The family stated that approximately 15 minutes after he received a bottle, the baby became cyanotic and subsequently lost consciousness. He was taken to the hospital immediately; however, he arrived lifeless. As this was a sudden death case, the child was referred to the Institute of Legal Medicine and Forensic Sciences in the city of Medellín to clarify the cause, manner, and mechanism of death.

The forensic autopsy revealed a eutrophic infant with central and peripheral cyanosis, without signs of trauma, and the internal examination found a single cardiac tumor in the anterior wall of the left ventricle. The mass was white and whorled; histological evaluation diagnosed a fibroma.

The manner of death was natural due to a cardiogenic shock caused by a primary tumor. *Acad Forensic Pathol.* 2017 7(1): 112-118

AUTHORS

Carolina Dominguez MD, University of South Florida - Pathology and Cell Biology

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, general supervision, writing assistance and/or technical editing.

Ashley Perkins DO MS, University of South Florida - Pathology and Cell Biology

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, writing assistance and/or technical editing.

Alexandra Duque MD, National Institute of Legal Medicine and Forensic Sciences Medellín Colombia

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, coordinated funding acquisition, writing assistance and/or technical editing.

Viagnney Bravo MD, National Institute of Legal Medicine and Forensic Sciences Medellín Colombia

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, coordinated funding acquisition, general supervision, general administrative support, writing assistance and/or technical editing.

CORRESPONDENCE

Carolina Dominguez MD, 12901 Bruce B Downs Blvd Tampa FL 33620-9951, cdomingu@health.usf.edu

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

This work was presented at the 2016 NAME Annual Meeting. The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Sudden death, Primary heart tumor, Fibroma

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.013>

Submitted for consideration on 10 Oct 2016. Accepted for publication on 8 Dec 2016

INTRODUCTION

Primary cardiac tumors are rare in the pediatric population. When they do occur, most of these tumors are considered benign, with easily recognizable features. The most common variant is rhabdomyoma, followed by fibromas and teratomas. Published medical literature has also described vascular tumors, myxomas, and lastly, the pericardial teratoma, which comprises a minor percentage.

We present a 8-month-old male infant who suffered a sudden death due to a primary cardiac tumor within the anterior wall of the left ventricle; histopathologic sections revealed a fibroma.

CASE REPORT

A young male infant, 8 months old and without previous medical history, suddenly died in April 2009. The mother stated that at approximately 10:30 pm the baby received a bottle and 15 minutes later became cyanotic and lost consciousness. The infant arrived at the hospital at 11:16 pm, unconscious and with acral and central cyanosis. There, physicians began external monitoring and basic life resuscitation efforts; however, his condition did not improve as he was unresponsive to stimuli, audible heart and lung sounds could not be auscultated, and his pupils were fixed and dilated. Resuscitation efforts were then suspended and the infant was pronounced dead.

As this was a case of sudden death of an infant, it was decided to have a medicolegal autopsy performed. The infant was taken to the National Institute of Legal Medicine and Forensic Sciences in Medellín, Colombia in order to establish the cause, mechanism, and manner of death.

The medicolegal autopsy identified the body as that of a eutrophic (i.e., adequate nutritional status), male infant with generalized cyanosis without any external malformations or signs of trauma. A milky liquid was noted to be exiting the mouth and nose.

The infant's weights and measures were normal for age.

The internal examination revealed an intact pericardium without hemorrhage. The heart weighed 74 g and there was a deformity due to a well-circumscribed intramural mass in the anterior and inferior wall of the left ventricle (**Image 1**).

Cardiovascular examination was performed following the lines of blood flow of the heart revealing a non-patent foramen ovale, a tricuspid valve circumference of 5 cm, pulmonary valve circumference of 3.5 cm, mitral valve circumference of 4.5 cm, and an aortic valve circumference of 3 cm. There was a mass in the anterior and inferior wall of the left ventricle measuring 4.7 x 3 x 3.5 cm, causing a large wall deformity and compressing the intraventricular space (**Image 2**).

The mass was well-circumscribed, off-white, and whorled with a firm consistency (**Image 3**).

Detailed inspection of the other organs, including histopathologic and neuropathology examinations, found no other lesions, anatomical defects, or additional important gross and microscopic findings that would have contributed to the death of the infant. Toxicology studies were negative. Microbiology and metabolic studies were not performed.

At the completion of the autopsy, the heart was preserved for fixation and sections for microscopic examination were obtained. Histological evaluation of the tumor revealed a nonencapsulated neoplasm composed of bland fibroblasts and collagen, without atypia, and infiltrating and displacing the normal underlying myocardium (**Image 4**). A diagnosis of fibroma was made.

DISCUSSION

Primary cardiac tumors are infrequent amongst all age groups. The incidence varies between 0.0017 to 0.28% with more than 90% having a benign histology. The most common variant in the pediatric population is rhabdomyoma (45-70%) and 60% of these cases are in patients with tuberous sclerosis. The next most frequently encountered primary tumors include fibromas (6-25%), teratomas (2-10%), vascular tumors, myxo-

mas, and finally the pericardial teratoma, which comprises a minor percentage (1).

Cardiac tumors, including fibromas, can cause multiple symptoms including those associated with outflow obstruction, interference of the function of the valves, arrhythmias, syncopal episodes, and sudden death. The clinical presentation is related to the size and location of the tumor. The signs and symptoms encountered occur in the following frequency: asymptomatic (63%), murmur (10%), arrhythmias (9%), seizures (5%), cyanosis, respiratory distress and cardiac insufficiency (4%), family history of tuberous sclerosis (3%), hydrops fetalis (2%), polyhydramnios (1%), and cerebral embolism (0.9%) (1-4).

Sudden death occurs from cardiac tumors when they involve critical structures in the heart. It has been described to occur unexpectedly in individuals in good health and without symptoms and in those who show slight symptoms of illness 24 hours prior to death. Sudden infant death syndrome is diagnosed with a prevalence between 0.17 and 1.5 per 1000 live births, followed by undiagnosed neoplasms (primary cardiac tumors and primary neoplasms of the nervous system), along with occult cardiac anomalies, intracranial hemorrhage, and infections (5). The mechanism of death from primary cardiac tumors is by obstruction of the atrioventricular orifices (outflow tract obstruction) (2), anomalies of the cardiac conduction system, and myocardial infarcts by emboli (5).

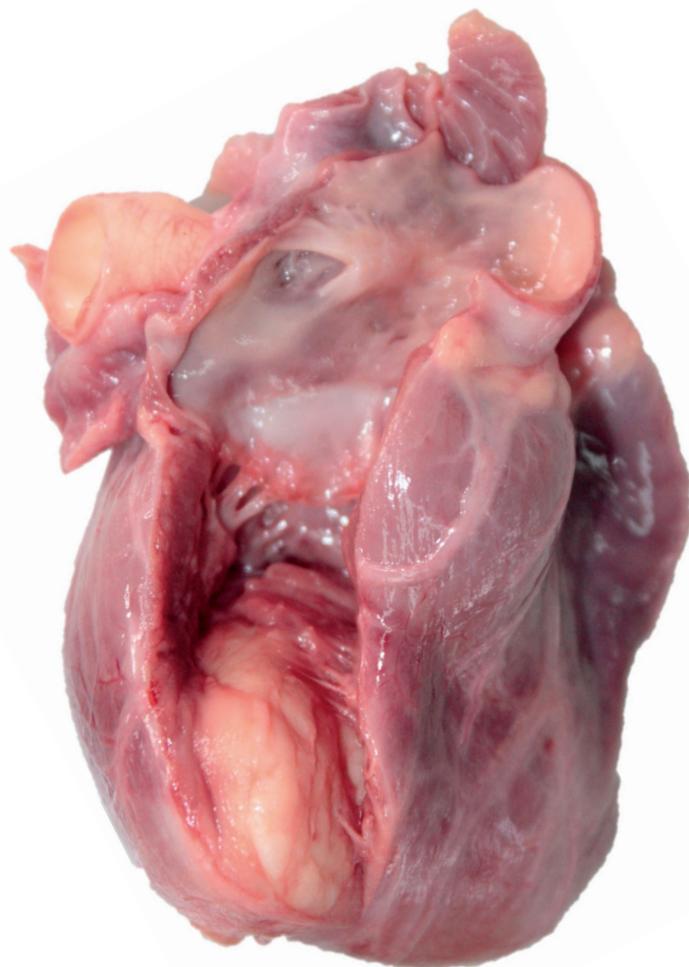


Image 1: Incision through the lateral left ventricle wall. Intramural mass within the anterior and inferior wall of the left ventricle.

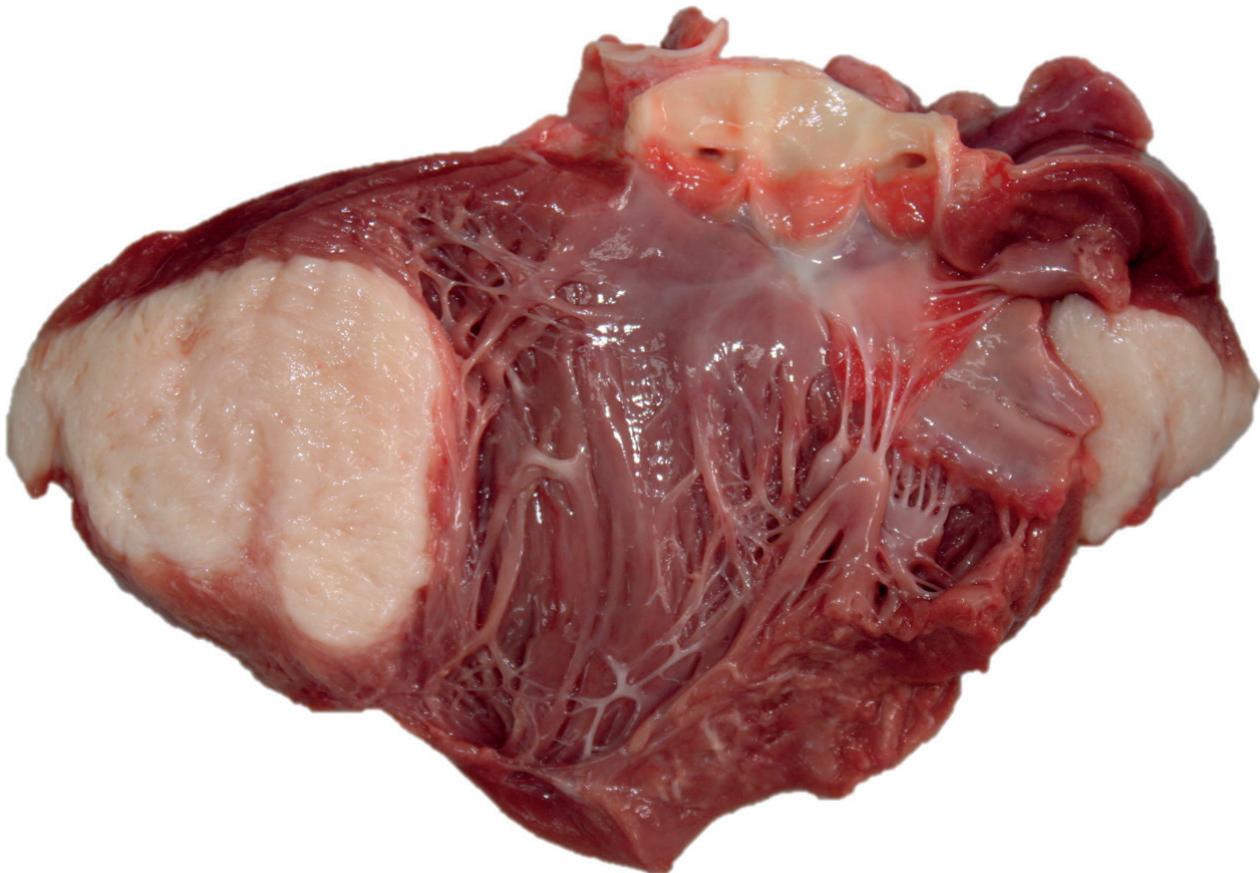


Image 2: Internal view, depicting the anterior and inferior left ventricle wall with a well-circumscribed mass.



Image 3: Cross-section of intramural mass within the anterior wall of the left ventricle.

Rhabdomyomas comprise 45% of primary cardiac tumors in infants and 53% of the benign primary cardiac tumors in the pediatric population. They are associated with tuberous sclerosis (Bourneville disease) in 60–75% of cases. Tuberous sclerosis is an autosomal dominant neurocutaneous syndrome that manifests with mental retardation, seizures, benign tumors in the brain and other organs, and hypopigmentation of the skin with presence of the disease also in one of the family members (2, 6, 7).

Histologically, rhabdomyomas are comprised of large polygonal cells with cytoplasmic vacuoles full of glycogen. The mass is lobulated, white and often small with a shiny or aqueous cut surface; a few hemorrhages and calcifications are commonly found. Multiple small tumors may be present and often occur in the

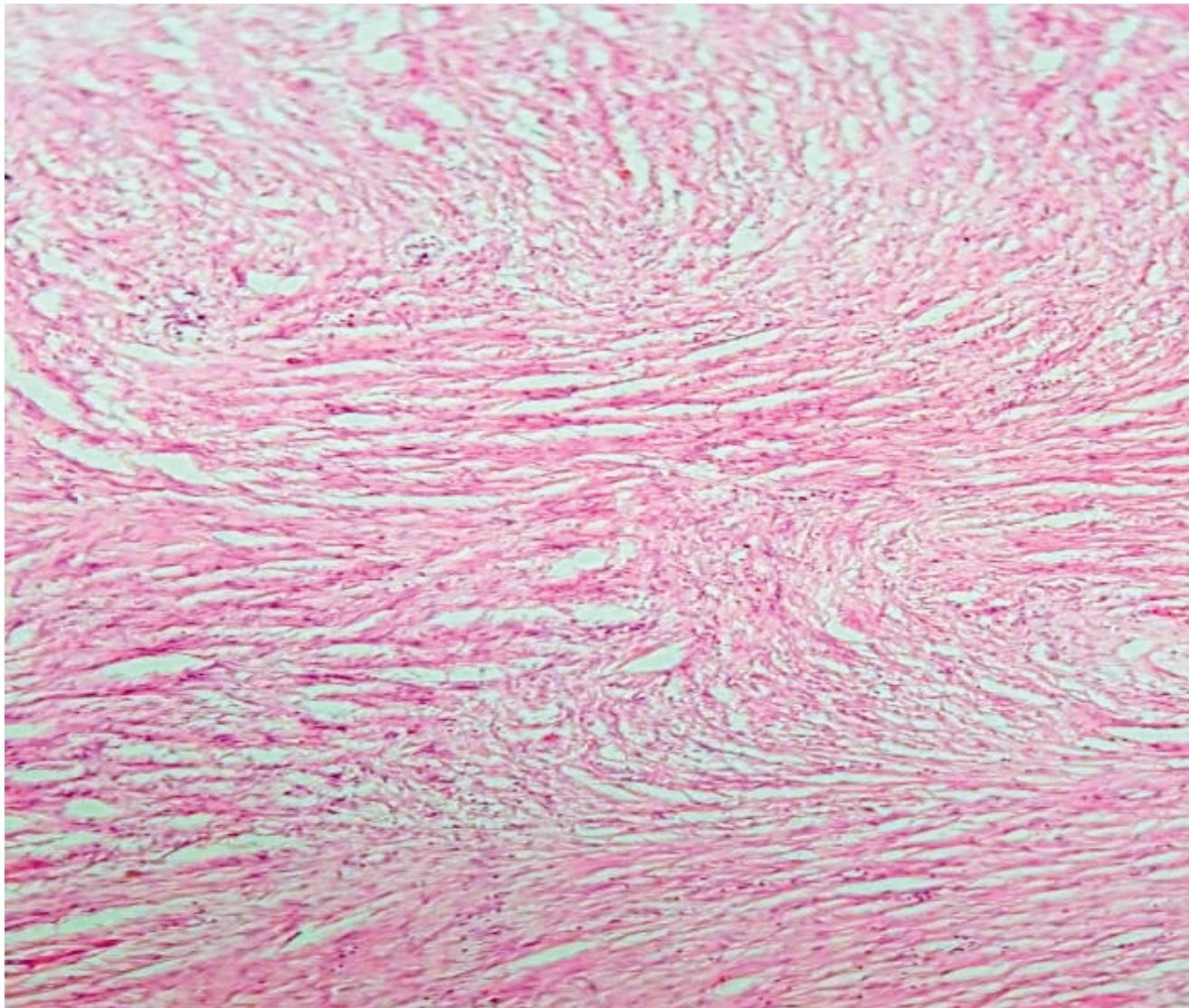


Image 4: Microscopic findings: bland fibroblasts and collagen (H&E, x40).

left ventricle or in the interventricular septum. When there are multiple tumors, this is often associated with tuberous sclerosis and presents as an outflow tract obstruction. A large number of these tumors spontaneously regress particularly if they occur in the first two years of life. The mechanism responsible for regression, according to the literature, is apoptosis (2).

Cardiac fibromas are solitary, well-circumscribed intramural lesions that are homogenous white in color; they represent 6-25% of pediatric primary cardiac tu-

mors. These tumors originate from fibroblasts of the connective tissue and the majority are located in the free wall of the left ventricle or the intraventricular septum. Histological examination shows an unencapsulated neoplasm composed of fusiform cells without atypia that infiltrate and displace the normal underlying myocardium. There may be areas of calcification and occasional foci of necrosis or areas of cystic degeneration due to its large growth. While histologically benign, these do not spontaneously regress, unlike rhabdomyomas. Depending on its size, these can ob-

struct blood flow within the heart, interfere with the function of the valves, and compromise the conduction system, leading to ventricular arrhythmias, syncope, or sudden death. Fibromas require early surgical treatment and those that do receive this early treatment have a good prognosis (3, 8-10).

Fibromas can occur in the autosomal dominant disorder, Gorlin-Goltz syndrome (characterized by basal cell carcinomas) in 3-5% of cases (10, 11).

Pericardial teratomas are benign tumors that usually present with pericardial hemorrhage or hydrops fetalis. Histologically, elements from all three germ layers may be identified along with multicystic areas and calcifications. These are surgically managed with a high rate of survival occurring after treatment. Even though they have been reported to recur, they are stable or may even regress (1).

Cardiac myxomas are the most common adult primary cardiac tumor. These soft, pale polypoid masses commonly form in the left atrium at the fossa ovale and often lead to valvular obstruction and arrhythmias. Microscopically, they are comprised of stellate cells with eosinophilic cytoplasm and indistinct cell borders within a myxoid stroma with variable fibrosis and calcifications identified. Most of these cases are sporadic, however, 10% are associated with Carney syndrome (12, 13).

Fetal echocardiography and magnetic resonance imaging (MRI) are techniques utilized to diagnose cardiac tumors in utero while echocardiography, cardiac catheterization, and magnetic resonance angiography have greater diagnostic efficacy in the postnatal period. Magnetic resonance imaging supplements the echocardiogram when the results obtained are suboptimal and permits a detailed assessment of the tumor, a better characterization of the tissue, and narrows the differential diagnosis on histopathologic analysis (14). Additionally, it provides a better assessment of the tumor's size, mural wall infiltration, and whether there is extension into the great vessels. The majority of the clinicians prefer echocardiogram in pediatric population, while the MRI has a fundamental role in

the adult (1, 11). These imaging techniques provide clinicians the opportunity to surgically intervene prior to cardiovascular compromise, thus preventing sudden death.

The treatment for cardiac fibromas may require non-radical surgical resection for those patients that present with outflow obstruction and arrhythmias; however, the preferred approach is follow-up echocardiograms in asymptomatic patients, as these characteristically spontaneously regress (9). Some fibroma tumors are managed conservatively, especially when the tumor is large (15).

CONCLUSION

Primary cardiac tumors are tumors that originate in the heart; these are rare in infancy. The majority of these tumors are benign (90-97%) and the effect they have on hemodynamics depends on their size and location. Of these tumors, fibromas are the second most common variety encountered amongst infants only after rhabdomyomas. Fibromas usually present as a solitary unencapsulated lesion located in the free wall of the left ventricle or in the septum. While these are histologically benign, spontaneous remission is a rare occurrence. Although they do not invade, they can become very large in size thus compromising proper hemodynamics and increasing mortality risk (1). Early diagnosis is possible with the help of imaging; however, the majority of patients are asymptomatic. Therefore, sudden death may be the first and only sign of their presence (5). This occurs after compromising the outflow tract when in the left ventricle or when the conduction system is involved, creating a fatal ventricular arrhythmia.

The incidence, prevalence, and mortality associated with these tumors amongst other causes of sudden death is unknown. Upon further analysis, research revealed very few cases reported within the national and international literature. The presented case is an illustration of a young infant without previously known medical history with a primary cardiac tumor that presented with sudden death.

In order to determine the cause of a sudden and unexpected death in an infant, correlation of the pre- and postnatal history along with the perimortem circumstances and any findings of the medicolegal autopsy that explain the physiopathological process that lead to death are required. We also emphasize the importance of the role of radiologic imaging techniques, such as fetal echocardiogram, that provide early diagnosis prior to symptoms suggestive of endstage cardiovascular compromise appear and aids in the histopathologic differential so that early surgical intervention can be made, if necessary, thus preventing sudden death from these tumors.

REFERENCES

- 1) Sánchez Andrés A, Insa Albert B, Carrasco Moreno JI, Cano Sánchez A, Moya Bonora A, Sáez Palacios JM. Tumores cardíacos primarios en la infancia. *An Pediatr (Barc)*. 2008; 69(1):15-22. Spanish. <https://doi.org/10.1157/13124213>.
- 2) Verhaaren HA, Vanakker O, De Wolf D, et al. Left ventricular outflow obstruction in rhabdomyoma of infancy: meta-analysis of the literature. *J Pediatr*. 2003 Aug; 143(2):258-63. PMID: 12970643. [https://dx.doi.org/10.1067/S0022-3476\(03\)00250-6](https://dx.doi.org/10.1067/S0022-3476(03)00250-6).
- 3) Burke A, Virmani R. Pediatric heart tumors. *Cardiovasc Pathol*. 2008 Jul-Aug; 17(4):193-8. PMID: 18402818. <https://dx.doi.org/10.1016/j.carpath.2007.08.008>.
- 4) Joly JM, Fuisz AR, Weissman G. Left ventricular fibroma presenting as syncope and ventricular tachycardia. *Echocardiography*. 2013 Aug; 30(7):E195-7. PMID: 23557255. <https://dx.doi.org/10.1111/echo.12204>.
- 5) Somers GR1, Smith CR, Perrin DG, et al. Sudden unexpected death in infancy and childhood due to undiagnosed neoplasia: an autopsy study. *Am J Forensic Med Pathol*. 2006 Mar; 27(1):64-9. PMID: 16501353. <https://dx.doi.org/10.1097/01.paf.0000203267.91806.ed>.
- 6) Sciacca P, Giacchi V, Mattia C, et al. Rhabdomyomas and tuberous sclerosis complex: our experience in 33 cases. *BMC Cardiovasc Disord*. 2014 May 9; 14:66. PMID: 24884933. PMCID: PMC4039990. <https://dx.doi.org/10.1186/1471-2261-14-66>.
- 7) Cotaina GL, Lázaro GE, Jiménez MI, et al. [Diagnosis of cardiac rhabdomyoma in the first trimester of pregnancy]. *Ginecol Obstet Mex*. 2016 Mar; 84(3):180-5. Spanish. PMID: 27424444.
- 8) Isaacs H Jr. Fetal and neonatal cardiac tumors. *Pediatr Cardiol*. 2004 May-Jun; 25(3):252-73. PMID: 15360117. <https://dx.doi.org/10.1007/s00246-003-0590-4>.
- 9) Jacobs JP, Konstantakos AK, Holland FW, et al. Surgical treatment for cardiac rhabdomyomas in children. *Ann Thorac Surg*. 1994 Nov; 58(5):1552-5. PMID: 7979700. [https://doi.org/10.1016/0003-4975\(94\)91963-1](https://doi.org/10.1016/0003-4975(94)91963-1).
- 10) Gotlieb AI. Cardiac fibromas. *Semin Diagn Pathol*. 2008 Feb; 25(1):17-9. PMID: 18350918. <https://doi.org/10.1053/j.semdp.2007.12.002>.
- 11) Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S. Pediatric cardiac tumors: clinical and imaging features. *Radiographics*. 2014 Jul-Aug; 34(4):1031-46. PMID: 25019440. <https://dx.doi.org/10.1148/rg.344135163>.
- 12) Bigelow NH, Klinger S, Wright AW. Primary tumors of the heart in infancy and early childhood. *Cancer*. 1954 May; 7(3):549-63. PMID: 13160940. [https://doi.org/10.1002/1097-0142\(195405\)7:3%3C549::aid-cncr2820070315%3E3.0.co;2-0](https://doi.org/10.1002/1097-0142(195405)7:3%3C549::aid-cncr2820070315%3E3.0.co;2-0).
- 13) Mercado-Guzman MP, Meléndez-Ramírez G, Castillo-Castellon F, Kimura-Hayama E. [Evaluation of cardiac tumors by multidetector computed tomography and magnetic resonance imaging]. *Arch Cardiol Mex*. 2016 Oct - Dec; 86(4):335-349. Spanish. PMID: 27210274. <https://dx.doi.org/10.1016/j.acmx.2016.04.005>.
- 14) Freedberg RS, Kronzon I, Rumancik WM, Liebeskind D. The contribution of magnetic resonance imaging to the evaluation of intracardiac tumors diagnosed by echocardiography. *Circulation*. 1988 Jan; 77(1):96-103. PMID: 3335075. <https://doi.org/10.1161/01.cir.77.1.96>.
- 15) Massin M, Ould AF, Jacquemart C, Damry N. Long-term conservative management of a giant cardiac fibroma. *Acta Cardiol*. 2013 Oct; 68(5):513-5. PMID: 24283114. <https://dx.doi.org/10.2143/AC.68.5.2994476>.

Blastomycosis in Wisconsin: Beyond the Outbreaks

Katrina Thompson, Alana K. Sterkel, Erin G. Brooks

ABSTRACT

In the summer of 2015, many individuals visiting the Little Wolf River in Waupaca County were exposed to the pathogenic fungus, *Blastomyces*. Over time, 59 confirmed and 39 probable cases were reported to the Wisconsin Department of Health Services (W-DHS), making this one of the largest outbreaks in recent state history. Though most instances of blastomycosis are not associated with common source outbreaks, cases such as this highlight the need for vigilance regarding this preventable cause of death. In the state of Wisconsin, an average of 118.6 cases (range, 84-174) of confirmed blastomycosis are diagnosed annually; the majority of these cases are sporadic rather than outbreak-associated. In the current study, we review characteristics of blastomycosis cases diagnosed at our academic medical center, as well as examine statewide W-DHS data, in order to familiarize pathologists with the epidemiologic and histologic characteristics of this disease. *Acad Forensic Pathol.* 2017 7(1): 119-129

AUTHORS

Katrina Thompson MD, University of Wisconsin Hospital and Clinics - Department of Pathology and Laboratory Medicine

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, writing assistance and/or technical editing.

Alana K. Sterkel PhD, University of Wisconsin Hospital and Clinics - Department of Pathology and Laboratory Medicine

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, writing assistance and/or technical editing.

Erin G. Brooks MD, University of Wisconsin Hospital and Clinics - Department of Pathology and Laboratory Medicine

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, general supervision, general administrative support, writing assistance and/or technical editing.

CORRESPONDENCE

Katrina Thompson MD, 1111 Highland Ave, Madison WI 53705, KThompson5@uwhealth.org

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

This work was presented at the 2016 NAME Annual Meeting. The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Blastomycosis, Blastomyces, Wisconsin, Outbreak

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.014>

Submitted for consideration on 8 Dec 2016. Accepted for publication on 20 Dec 2016

INTRODUCTION

The *Blastomyces* genus is comprised of two pathogenic dimorphic fungal species: *B. dermatitidis* and *B. gilchristii*. Both species are endemic east of the Mississippi river from Wisconsin to Louisiana and as far east as northern Maine (1). The organism is known to reside in the soil, but becomes aerosolized around lakes and rivers. In addition to humans, it can infect many different hosts including animals such as dogs. Inhalation is the most common way to acquire blastomycosis; transmission from person to person is uncommon, but can be seen, particularly transplacentally between mother and fetus or between partners during sexual intercourse (2). Rarely, direct inoculation of the skin has occurred during autopsies when pathologists have injured themselves and unintentionally contaminated the wounds with infected patient tissue (3). The clinical manifestations can be quite variable, ranging from asymptomatic to rapidly severe and fatal respiratory distress. Many factors are thought to contribute to clinical severity including inoculation level, time to treatment, and underlying health and immune status. Disseminated disease can also arise and may involve sites such as the skin, bone, genitourinary tract, and central nervous system (4). Although not a nationally notifiable disease, blastomycosis is endemic in the state of Wisconsin and has been designated as a reportable disease since two major outbreaks occurred in 1984 (5). Other states in which blastomycosis is a reportable disease include Arkansas, Louisiana, Michigan, and Minnesota (1).

METHODS

A retrospective search of the University of Wisconsin Hospital and Clinics electronic databases including PowerPath (Sunquest Informational Systems), McKesson Information Systems, and Healthlink (Epic) was conducted for tissue samples, autopsies, cultures, and clinical information for patients positive for blastomycosis. Cases were retrieved from years 2003–2015 using search terms “blastomycosis,” “*Blastomyces*,” and “*B. dermatitidis*.” Until 2014, forensic pathology autopsy reports at our institution were maintained in a separate nonelectronic database; this separate forensic

report database was manually searched for confirmed blastomycosis cases from 2003–2014. Data were compiled concentrating on age at diagnosis, gender, race/ethnicity, comorbidities, method of diagnosis, morbidity and mortality due to *Blastomyces* infection, and date of initial diagnosis. Finally, statewide blastomycosis epidemiologic data provided by the Wisconsin Department of Health Services (W-DHS) from the years 2003–2015 were reviewed; a confirmed case of blastomycosis as defined by W-DHS required either isolation of *Blastomyces* spp. or visualization of the characteristic broad-based budding yeast from a patient sample.

RESULTS

University of Wisconsin Hospital and Clinics Data

Between 2003 and 2015, 82 confirmed cases of blastomycosis were diagnosed from culture and/or tissue samples obtained at the University of Wisconsin Hospital and Clinics (average annual number of cases, 6.31). Of these, 42 were diagnosed via culture only, 20 via tissue samples only (skin, lung, or other), and 20 via both culture and tissue samples. Demographics, comorbidities, and date of diagnoses are reported in **Table 1**. Review of medical records revealed that ten patients died due to blastomycosis, two of which were autopsied. **Table 2** outlines specific demographics, comorbidities, and date of diagnosis of those who died due to blastomycosis. The fatality rate of blastomycosis cases diagnosed by tissue was 12.2%. Autopsy findings were reviewed in both cases.

Autopsy Case 1:

An immunocompetent 21-year-old man without significant medical history participated in a Little Wolf River (Waupaca County, WI) rafting trip in July of 2015. He was diagnosed with blastomycosis in August, but declined antifungal treatment until November of 2015, at which point he was hospitalized with severe respiratory distress. He was ultimately placed on extracorporeal membrane oxygenation and antifungal medication. He developed metabolic abnormalities that led to acute toxic metabolic encephalopathy and he died.

At autopsy, the lungs were markedly heavy and consolidated, with multifocal hemorrhage (**Image 1**). Following formalin fixation, a focal miliary pattern of granulomas was evident (**Image 2**). Microscopic sections revealed diffuse interstitial and intra-alveolar organizing fibrosis, with scattered hyaline membranes and type II pneumocyte hyperplasia (**Image 3A**). All lung lobes were involved by this exuberant diffuse alveolar damage and organizing pneumonia. There were also geographic areas of intra-alveolar hemorrhage, necrosis, cavitation, and acute thromboemboli within distal vessels. Admixed with the areas of organizing fibrosis were numerous histiocytes and giant cells containing round, encapsulated, broad-based budding yeast that appeared morphologically consistent with blastomycosis (**Images 3B and 3C**).

Autopsy Case 2:

An immunocompromised 68-year-old man with a history of renal transplantation secondary to diabetic nephropathy was admitted six months prior to death due to diffuse viral (varicella zoster and cytomegalovirus) and fungal (*Aspergillus*) pneumonia. His medical history was significant for type 2 diabetes mellitus, hypertension, congestive heart failure, atrial fibrillation, and a prosthetic aortic valve. Complications during hospitalization resulted in an above-the-knee amputation for staphylococcal osteomyelitis. He developed fever and dyspnea, and went into cardiac arrest. Although successfully resuscitated, he subsequently developed acute respiratory and multiorgan failure and died.

At autopsy, the lungs were markedly heavy, with focal consolidation and pulmonary bullae. Several small, white-tan nodules averaging 0.2–0.5 cm in diameter were scattered throughout the lung parenchyma. Acute antemortem thromboemboli were visualized within the small peripheral pulmonary arteries with corresponding wedge-shaped, tan colored distal infarcts. Microscopic sections revealed pneumonia, necrosis, and hemorrhage resulting in disruption of the alveoli. Numerous round, encapsulated, broad-based budding yeast, morphologically consistent with blastomycosis were also seen. Gross examination of the skin re-

Table 1: Demographics, Health Status, and Year of Diagnosis for Confirmed Blastomycosis

| | |
|--------------------------------------|-----------------|
| Average Age at Diagnosis | 45 (range 3-86) |
| Sex | |
| Male | 53 (65%) |
| Female | 29 (35%) |
| Race | |
| Caucasian | 58 (70%) |
| African American | 4 (5%) |
| Asian | 8 (10%) |
| Hispanic | 3 (4%) |
| American Indian | 1 (1%) |
| Unavailable | 8 (10%) |
| Comorbidities | |
| None | 31 |
| Transplant (solid organ) | 17 |
| Underlying lung disease | 9 |
| Infections (HIV, tuberculosis, etc.) | 6 |
| Diabetes Mellitus | 10 |
| Other Causes of Immune Suppression | 21 |
| Year | |
| 2003 | 7 |
| 2004 | 2 |
| 2005 | 5 |
| 2006 | 6 |
| 2007 | 6 |
| 2008 | 3 |
| 2009 | 10 |
| 2010 | 9 |
| 2011 | 4 |
| 2012 | 5 |
| 2013 | 5 |
| 2014 | 10 |
| 2015 | 10 |

Table 2: Demographics, Health Status, and Year of Diagnosis for Blastomycosis-Related Deaths

| | |
|--------------------------------------|------------------|
| Average Age at Diagnosis | 50 (range 21-76) |
| Sex | |
| Male | 7 (70%) |
| Female | 3 (30%) |
| Race | |
| Caucasian | 5 (50%) |
| Asian | 2 (20%) |
| Hispanic | 1 (1%) |
| Unavailable | 2 (20%) |
| Comorbidities | |
| None | 1 |
| Transplant (solid organ) | 6 |
| Underlying lung disease | 1 |
| Infections (HIV, tuberculosis, etc.) | 2 |
| Diabetes Mellitus | 2 |
| Other Causes of Immune Suppression | 1 |
| Year | |
| 2003 | 1 |
| 2004 | 2 |
| 2007 | 1 |
| 2010 | 2 |
| 2011 | 1 |
| 2012 | 1 |
| 2014 | 1 |
| 2015 | 1 |

vealed scattered ring-like gray lesions averaging 0.5 to 1.0 cm in diameter concentrated over the back and anterior chest wall. Microscopic examination of those lesions revealed normal cutaneous architecture without evidence of intracellular inclusions.

Wisconsin Department of Health Services Data

Between 2003 and 2015, the average number of confirmed cases of blastomycosis reported annually in the state of Wisconsin was 118.6 (range, 84-174). The majority of cases were sporadic; however, in four

years (2006, 2009, 2010, 2015) there were blastomycosis outbreaks (**Figure 1**). The most recent outbreak of blastomycosis arose among individuals who visited the Little Wolf River in Waupaca County, WI during the summer of 2015. To date, there have been 59 confirmed and 39 probable cases of blastomycosis—including the previously described fatality—associated with this outbreak.

Beginning in 2008, W-DHS began requesting more in-depth demographic, clinical, diagnostic, and exposure documentation for reported cases of blastomyco-



Image 1: Pulmonary blastomycosis results in markedly heavy lungs with numerous fibrous adhesions causing irregularity of the pleural surfaces. The patches of discoloration represent areas of hemorrhage and necrosis.

sis. Between 2008 and 2014, there were a total of 787 confirmed blastomycosis cases in Wisconsin. The majority of the patients were male (67%), and the median age of diagnosis was 46 years (range, 3-97 years). The symptoms most commonly reported were cough and/or fatigue (75%), fever/chills/night sweats (50%), and skin lesions (25%). In 44% of cases (n=346), inpatient hospitalization was required and the annual fatality rate was 5.6% (range, 3.2-11.2%). One caveat is that while reporting of blastomycosis is mandatory in

the state of Wisconsin, reporting of whether or not a confirmed case results in death is not. Thus, the above fatality rates only represent those deaths that were voluntarily reported.

DISCUSSION

The diagnosis of blastomycosis may not be clinically suspected as the disease manifestations can vary widely. One larger retrospective study found that



Image 2: White, firm, granulomatous lesions are common within *Blastomyces* infected organs. Within the lungs, granulomas can vary in size and may be either focal or diffuse in a miliary pattern (as seen above). Formalin fixation can increase tissue contrast, allowing for better visualization of small granulomas.

the diagnosis was correctly suspected at initial clinical evaluation in only 18% of patients (6). The most common misdiagnoses included lung tumor and/or metastatic disease, pneumonia, and tuberculosis (7). Given that the disease is often unsuspected, microbial culture samples may not be submitted, necessitating diagnosis by morphologic evaluation of tissue samples obtained via biopsy or autopsy. As shown in the current study, even in endemic states such as Wisconsin, the majority of blastomycosis cases are sporadic rather than associated with well-publicized outbreaks, and case history may not be particularly helpful in suggesting the diagnosis. Our data suggest that while the median age of blastomycosis diagnosis is 45 years, the disease should be considered in all age groups ranging from pediatric to geriatric and

that patients need not be immunocompromised to become infected. Of the patients at our institution infected with *Blastomyces*, 40% had no clinical history or comorbidity that would cause immunosuppression or opportunistic infection opportunities. The other 60% had some sort of immunosuppression either iatrogenic (e.g., solid organ transplant undergoing transplant rejection prevention, chemotherapy, or corticosteroid treatment for other underlying disorders), concurrent infections (e.g., human immunodeficiency virus, tuberculosis), or medical conditions (e.g., underlying lung disease or diabetes mellitus). Men are more likely to be affected than women; more than two-thirds of the patients were male in our study. This male predominance has also been noted in other studies; it is theorized that this is likely multifactorial and may be

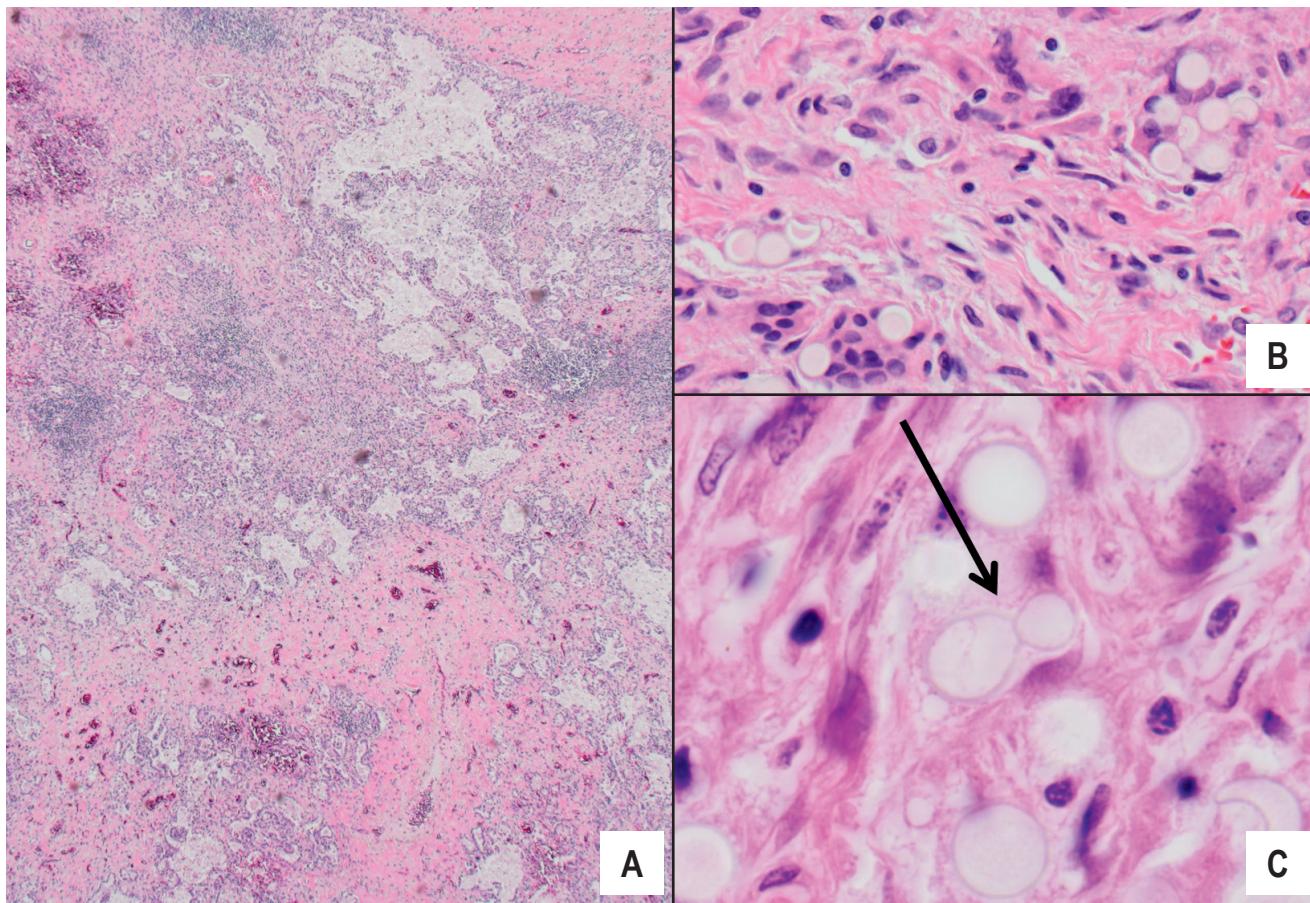


Image 3: Microscopic lung sections showing: **A)** Diffuse interstitial and intra-alveolar organizing fibrosis, scattered hyaline membranes, intra-alveolar hemorrhage, and necrosis (H&E, x40), **B)** Histocytes and giant cells containing round, encapsulated, yeast (H&E, x400), and **C)** The characteristic broad-based budding (arrow) associated with *Blastomyces* (H&E, x1000).

attributable to the increased likelihood of men participating in outdoor activities, either recreationally or occupationally (2, 8).

Epidemiologic clues that should raise the suspicion for blastomycosis include travel or residence in an endemic/hyperendemic area, participation in outdoor activities involving exposure to soil and wetlands, and recent onset of pulmonary or flu-like symptoms (8). As the disease incubation period ranges from three weeks to three months, it may challenging to correlate disease onset with a particular exposure (5). As shown by our study, there can be wide geographic variation

of blastomycosis incidence within a single state. For instance, our institution is located within Dane County, WI—a nonhyperendemic region. Annually, we diagnose six to seven cases of blastomycosis via culture or morphologic assessment of tissue, and our county's average annual incidence rate of blastomycosis is one per 100 000 persons. The hyperendemic counties of northern Wisconsin have an average annual incidence rate of greater than ten per 100 000 persons. Due to the nonspecific clinical presentation of blastomycosis, patients may be inappropriately treated with antibiotics, even in endemic states. Blastomycosis should thus be considered in the differential diagnosis of patients

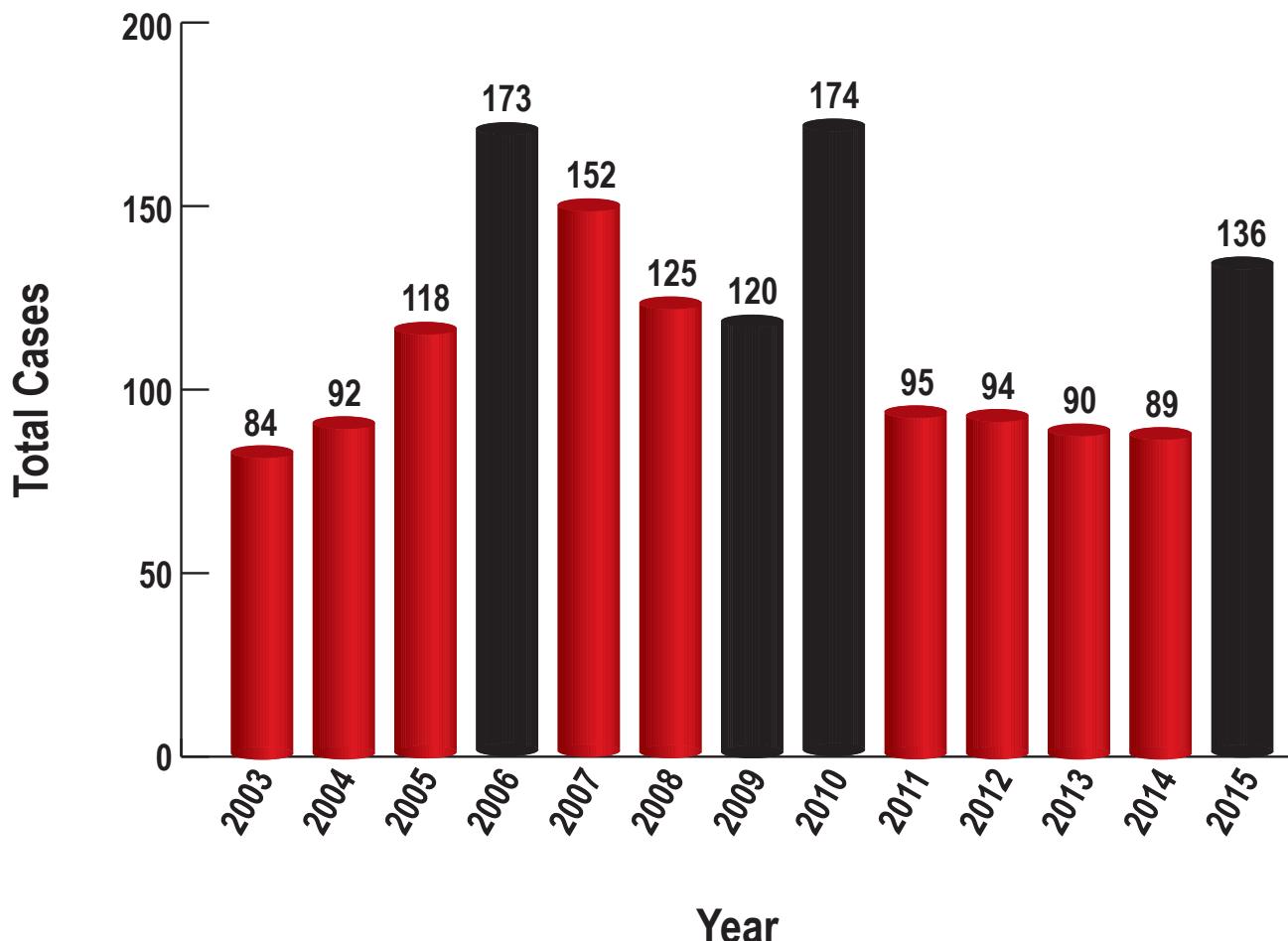


Figure 1: Confirmed cases of blastomycosis in the state of Wisconsin between 2003 and 2015. Bars in black represent years with known outbreaks (2006, 2009, 2010, 2015).

expiring of pulmonary illness unresponsive to antibiotic therapy (8). As dogs have a relatively high rate of blastomycosis infection, a history of the recent death of a pet dog due to a pulmonary illness may indicate a possible common source *Blastomyces* exposure; however, blastomycosis is not transmitted between species (8, 9). Finally, there may be racial and/or ethnic predispositions to blastomycosis: a study of Marathon County found that of the 55 patients who contracted blastomycosis during the 2009-2010 outbreak, 45% were Hmong. This ethnic clustering was ultimately deemed to be multifactorial, but further investigation into a possible genetic predisposition is currently underway (10). Our data showed a predominance of infection within the Caucasian population (approximately 70%), which more likely is representative of our general population demographics rather than an ethnic predisposition.

Given that the clinical manifestations can be variable and case history noncontributory, having a good working knowledge of the morphology of blastomycosis and its mimics can be essential. Characteristically, blastomycosis is found in the yeast rather than hyphal form at human body temperatures. The yeast is round, 8-15 μm in diameter, encapsulated, and clear, with broad-based budding (9, 11). Alveolar macrophages assimilate the yeast in an attempt to destroy it, but in fact provide it a safe and environmentally controlled setting to replicate. The exact mechanism by which *Blastomyces* is able to evade the natural immune system is not fully understood, but surface proteins such as BAD-1 and α 1-3 glucan may play a significant role (2, 11, 12). The other two organisms that may resemble blastomycosis are *Paracoccidioides brasiliensis*, a dimorphic fungus endemic in Central and South America, and *Cryptococcus neoformans*, a ubiquitous environmental fungus found worldwide. *Paracoccidioides*, as compared to *Blastomyces*, has a thinner cell wall, more polymorphic shape, and may show circumferential small buds surrounding the parent yeast (the so-called "mariner's wheel" appearance). *Cryptococcus* has a thick mucicarmine-positive mucoid capsule, as opposed to the thin or incomplete mucicarmine capsular staining that may occasionally be seen with *Blastomyces* (9).

While nonspecific, gross features supportive of blastomycosis infection include those pulmonary findings reported in the two previously described autopsy cases such as consolidation and hemorrhage; granulomatous lesions are often visible and can be either focal or diffuse (4). Pleural adhesions and hilar adenopathy are also common. Upon sectioning of the lungs, areas of edema, hemorrhage, and cavitary necrosis may be seen. Cutaneous manifestations are also common; the lesions are characteristically round, may be single or multiple, and vary in size from 0.5-1.5 cm in diameter. They tend to appear raised with a violaceous, verrucous, arciform border, while the center of the lesion is pustular and often has crust formation (**Image 4**) (13, 14). Histologically, lesions show hyperplasia of the epidermis with neutrophilic and granulomatous infiltrate of the dermis. The degree of histologic changes in skin can vary widely (as demonstrated in the second autopsy case) and lesions grossly consistent with blastomycosis infection may not be easily recognized histologically. The use of special stains such as such as Periodic acid-Schiff with/without diastase (PAS/PAS-D) or Grocott's/Gomori Methenamine Silver (GMS), can be beneficial (**Image 5**). In general, most of the antemortem blastomycosis testing modalities are also available for postmortem samples. A comparison of testing options, including relative costs, turnaround times, and required samples is given in **Table 3**.



Image 4: Gross image of a verrucous cutaneous *Blastomyces* lesion. The lesions are characteristically round, pustular, and vary in size from 0.5-1.5 cm in diameter.

CONCLUSION

As blastomycosis is not a nationally notifiable disease, epidemiologic patterns of infection have yet to be fully characterized. Review of data from states with mandatory reporting, such as Wisconsin, can thus contribute greatly to the understanding of this disease. The average number of confirmed cases per year in our state is 118.6; in at least 44% of these, inpatient hospitalization is required; annually, 5-6% are fatal. These figures likely underestimate the actual disease morbidity/mortality as reporting of the disease

is mandatory in our state, but reporting of deaths is voluntary. Though most cases of blastomycosis are sporadic, the recent Little Wolf River outbreak illustrates that common source exposures continue to occur. It also reinforces the importance of timely institution of antifungal therapy, as the one fatality arose in an otherwise immunocompetent young man who initially refused treatment. Untreated blastomycosis has a reported mortality rate of approximately 60-78% (2, 17). As blastomycosis is often not suspected clinically, morphologic assessment of tissue with or without microbial cultures is essential to postmortem exam-

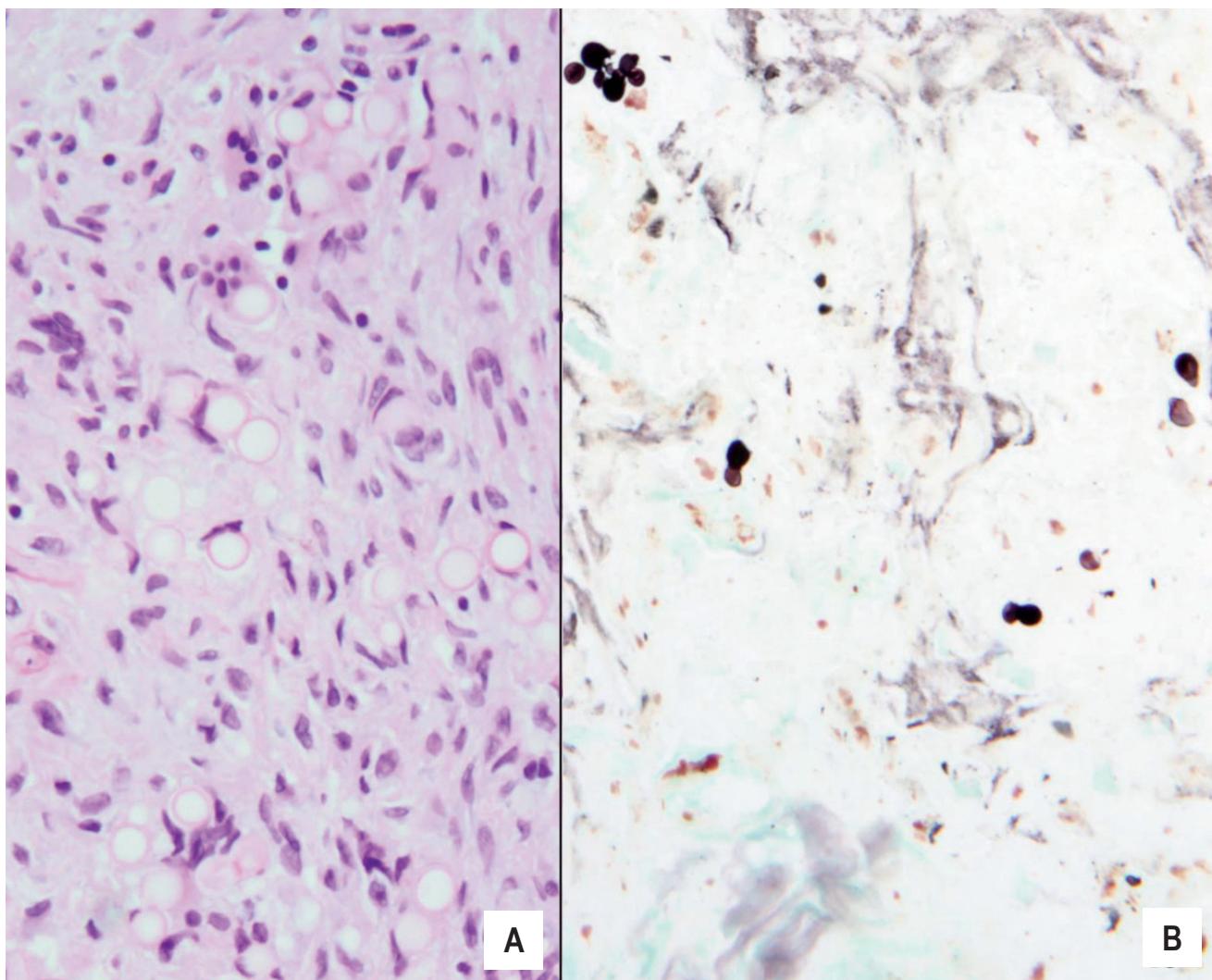


Image 5: Special stains available to better visualize *Blastomyces* in tissue section. **A)** Periodic acid-Schiff with diastase (PAS-D, x500), **B)** Grocott's/Gomori Methenamine Silver (GMS, x500).

Table 3: Summary of Common Postmortem Testing Available for *Blastomyces*

| Test | Sample Type | Turn Around Time | Price Range | Known Limitations |
|---|---|------------------|-------------|---|
| Stained slides (H&E*, PAS-D†, GMS‡) | Tissue | Days | \$106-183 | Infection burden affects visualization; exact identification sometimes difficult |
| Potassium hydroxide (KOH) mounts (Image 6) | Skin scrapping, pus, bronchial secretions | Hours | \$50-60 | Correct deep sampling important; high false negative rate |
| Culture | Tissue, blood, bronchial secretions, urine, CSF§ | Weeks | \$75-85 | Requires collection under sterile conditions |
| Antibody/Antigen | Blood, urine, CSF | Days | \$54-111 | Consistency of sample and storage temp critical; cross-reactivity common (15, 16) |
| 18/28S RNA Polymerase chain reaction (PCR) | Fresh and formalin-fixed tissue, blood, bronchial secretion, urine, CSF | Days | \$450-500 | Primary visualization of fungi needed |

* Hematoxylin and Eosin

† Periodic acid-Schiff with/without diastase

‡ Grocott's/Gomori Methenamine Silver

§ Cerebral spinal fluid

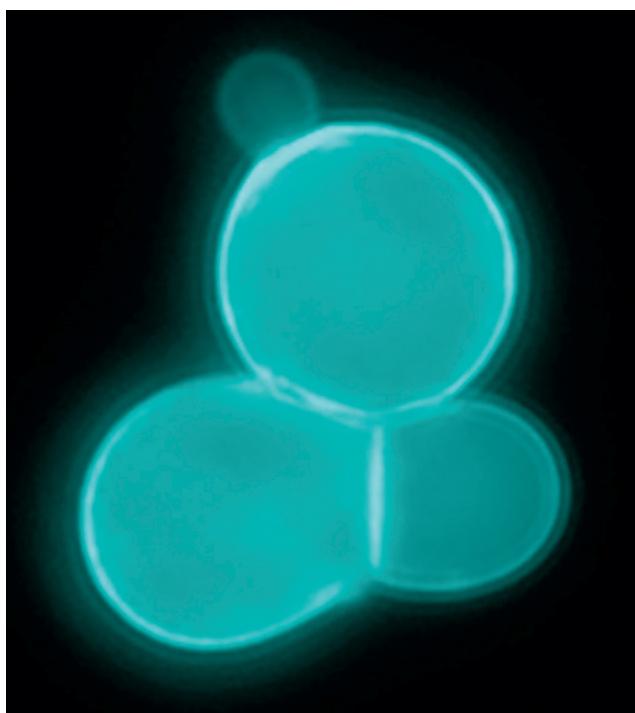


Image 6: Potassium hydroxide (KOH) mount of *Blastomyces* with calcofluor white staining visualized under fluorescent light (aqua color is computer generated). Notice broad-based budding of yeast, which is characteristic of *Blastomyces*.

ination. At our academic institution, we diagnose six to seven cases of blastomycosis annually via culture or examination of biopsy and/or autopsy tissue. Overall, our study highlights the need for vigilance among pathologists regarding this preventable cause of death.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Gregory Gauthier from the University of Wisconsin for providing the cutaneous photo of *Blastomyces*.

REFERENCES

- 1) Centers for Disease Control and Prevention [Internet]. Atlanta: Centers for Disease Control and Prevention; c2015. Blastomycosis; [updated 2015 Dec. 5; cited 2016 Aug 31]. Available from: <http://www.cdc.gov/fungal/diseases/blastomycosis/index.html>.
- 2) Bariola RJ, Vyas KS. Pulmonary blastomycosis. *Semin Respir Crit Care Med.* 2011 Dec; 32(6):745-53. PMID: 22167402. <https://dx.doi.org/10.1055/s-0031-1295722>.
- 3) Larson, DM., Eckman MR, Alber RL, Goldschmidt VG. Primary cutaneous (inoculation) blastomycosis: an occupational hazard to pathologists. *Am J Clin Pathol.* 1983 Feb; 79(2):253-5. PMID: 6823911. <https://doi.org/10.1093/ajcp/79.2.253>.
- 4) Haque AK. Pulmonary pathology. Philadelphia: Churchill Livingstone/Elsevier; 2008. Chapter 12, Fungal diseases; p.219-44.
- 5) Centers for Disease Control and Prevention (CDC). Blastomycosis-Wisconsin, 1986-1995. *MMWR Morb Mortal Wkly Rep.* [Internet]. 1996 Jul 19 [updated 1996; cited 2016 Aug 31]; 45(28):601-3. Available from: <http://www.cdc.gov/mmwr/preview/mmwrhtml/00043101.htm>.

- 6) Lemos LB, Baliga M, Guo M. Blastomycosis: The great pretender can also be an opportunist. Initial clinical diagnosis and underlying diseases in 123 patients. *Ann Diagn Pathol.* 2002 Jun; 6(3):194-203. PMID: 12089732. <https://doi.org/10.1053/adpa.2002.34575>.
- 7) Saccente, M., Woods GL. Clinical and laboratory update on blastomycosis. *Clin Microbiol Rev.* 2010 Apr; 23(2):367-81. PMID: 20375357. PMCID: PMC2863359. <https://dx.doi.org/10.1128/CMR.00056-09>.
- 8) Pfaff BL, Agger WA, Volk TJ. Blastomycosis diagnosed in a nonhyperendemic area. *WMJ.* 2014 Feb; 113(1):11-8; quiz 19. PMID: 24712215.
- 9) Taxy JB. Blastomycosis: contributions of morphology to diagnosis: a surgical pathology, cytopathology, and autopsy pathology study. *Am J Surg Pathol.* 2007 Apr; 31(4):615-23. PMID: 17414110. <https://dx.doi.org/10.1097/01.pas.0000213389.47913.b8>.
- 10) Roy M, Benedict K, Deak E, et al. A large community outbreak of blastomycosis in Wisconsin with geographic and ethnic clustering. *Clin Infect Dis.* 2013 Sep; 57(5):655-62. PMID: 23735332. <https://dx.doi.org/10.1093/cid/cit366>.
- 11) Mycology Online [Internet]. Adelaide (Australia): University of Adelaide; c2016. Blastomyces dermatitidis; [updated 2016 July 18; cited 2016 Aug 31]. Available from: <http://www.mycology.adelaide.edu.au/mycoses/dimorphic/>.
- 12) Brandhorst TT, Rooney PJ, Sullivan TD, Klein BS. Using new genetic tools to study the pathogenesis of *Blastomyces dermatitidis*. *Trends Microbiol.* 2002 Jan; 10(1):25-30. PMID: 11755082. [https://doi.org/10.1016/s0966-842x\(01\)02258-2](https://doi.org/10.1016/s0966-842x(01)02258-2).
- 13) Balasaraswathy P, Theerthanath. Cutaneous blastomycosis presenting as non-healing ulcer and responding to oral ketoconazole. *Dermatol Online J.* 2003 Dec; 9(5):19. PMID: 14996392.
- 14) Busam KJ. Dermatopathology. 2nd edition. Philadelphia: Saunders Elsevier; c2015. Chapter 3, Infectious diseases of the skin p. 105-83.
- 15) ARUP Laboratories [Internet]. Salt Lake City: ARUP Laboratories; c2016. Blastomyces antibodies by CF and ID; [cited 2016 Aug 31]. Available from: <http://ltd.aruplab.com/Tests/Pub/0050626>.
- 16) MiraVista Diagnostics [Internet]. Indianapolis: MiraVista Diagnostics; c2016. Blastomyces quantitative EIA test; [cited 2016 Aug 31]. Available from: <http://miravistalabs.com/medical-fungal-infection-testing/antigen-detection/blastomyces-dermatitidis-quantitative-eia-test/>.
- 17) Sterkel AK. Subversion of innate immunity by blastomyces dermatitidis [dissertation]. Madison (WI): University of Wisconsin-Madison; 2014. 164 p.



Fatal Rotavirus Infection in a 4-Year-Old with Unsuspected Autoimmune Adrenal Insufficiency

Alison Krywanczyk, Elizabeth A. Bundock

ABSTRACT

The diagnosis of adrenal insufficiency is often delayed, as the presenting symptoms of fatigue, abdominal pain, and anorexia are vague and nonspecific. However, timely diagnosis and treatment with replacement steroids are needed to prevent fatal adrenal crisis. While the most common cause of primary adrenal insufficiency in childhood is congenital adrenal hyperplasia, a significant minority (13-23%) is caused by autoimmune destruction of the gland. We present a case of a 4-year-old, previously healthy child who had a one-day history of nausea and vomiting, and was found unresponsive by her caretaker. Despite emergency rescue and transport to the hospital, she was pronounced dead. At autopsy, the adrenal glands were atrophied. Histologic examination revealed lymphocytic infiltration of the adrenal glands consistent with autoimmune adrenal insufficiency. Fecal viral antigen testing was positive for rotavirus. The cause of death was determined to be adrenal crisis in the setting of rotavirus gastroenteritis due to adrenal insufficiency (Addison disease). *Acad Forensic Pathol.* 2017 7(1): 130-135

AUTHORS

Alison Krywanczyk MD, University of Vermont Medical Center

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

Elizabeth A. Bundock MD PhD, Office of Chief Medical Examiner - Vermont State Department of Health

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, general supervision, general administrative support, writing assistance and/or technical editing.

CORRESPONDENCE

Alison Krywanczyk MD, EP2 111 Colchester Ave., Burlington VT 05401, Alison.Krywanczyk@uvmhealth.org

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

This work was presented at the 2016 NAME Annual Meeting. The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Addison disease, Autoimmune, Pediatric, Rotavirus, Adrenal

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.015>

Submitted for consideration on 25 Nov 2016. Accepted for publication on 19 Dec 2016

INTRODUCTION

Adrenal insufficiency (AI) is an uncommon disease in adults and even more rare in children (1). However, prompt recognition and diagnosis of AI is needed to begin treatment and prevent a potentially fatal adrenal crisis (2). Adrenal insufficiency can be subdivided into either primary or secondary/tertiary. In primary AI, the production of mineralocorticoids and glucocorticoids is impaired due to destruction of the adrenal cortex. In contrast, secondary or tertiary AI results from diseases affecting the pituitary or hypothalamus. In these, the production of mineralocorticoids is usually intact because the renin-angiotensin-aldosterone pathway still functions; however, production of corticosteroids is impaired due to impaired production of adrenocorticotrophic hormone (ACTH) (3). Secondary AI is most common form of AI and is typically due to the abrupt withdrawal of pharmacologic treatment with corticosteroids (4).

The term “Addison disease” is nonspecific, referring to any chronic form of primary AI (2). While autoimmune adrenalitis (also known as idiopathic Addison disease) is the most common cause of primary AI in adults in developed countries, the most common cause of primary AI in children is congenital adrenal hyperplasia (CAH). However, a significant minority (13 to 23%) of primary AI in children is due to autoimmune adrenalitis. Unlike autoimmune AI, CAH most commonly presents in the neonatal period (1, 5) and it has been proposed that autoimmune AI is the most common cause of primary AI presenting after the neonatal period (6). We present a case report of a 4-year-old child with subclinical autoimmune adrenalitis who experienced a fatal adrenal crisis precipitated by rotavirus infection.

CASE REPORT

A 4-year-old previously healthy child was found unresponsive by her caregiver after a one- to two-day history of an illness characterized by nausea and vomiting. Emergency medical services were called and she was transported to the hospital where she was pronounced dead after attempted resuscitation.

Autopsy revealed an underweight, otherwise well-developed 4-year-old. Weight-for-stature was 3rd percentile, while weight-for-age was 25th percentile. No areas of hyperpigmentation on the skin were observed. The right and left adrenal glands were markedly atrophic, weighing less than 1 g each (expected combined weight of 6 g). The pituitary, pancreas, and thyroid glands were grossly unremarkable.

Microscopic evaluation of the adrenals showed lymphoplasmacytic inflammation (**Image 1**) consisting predominantly of T cells with a slight predominance of CD8 to CD4 positive cells. Focal follicle formation by CD20 positive B cells was also observed (**Image 2**).

The contents of the small intestine were mucoid and bilious. Microscopic examination showed superficial necrosis of the mucosa, with increased lymphocytes in the lamina propria. The pancreas was microscopically unremarkable.

Postmortem serum cortisol was 1 µg/dL (reference range, 3-22 µg/dL). Fecal viral antigen testing detected rotavirus. Vitreous sodium was 136 mmol/L and vitreous glucose was <35 mg/dL. Hemoglobin A1C was 5.2%.

The gross and histologic features of the adrenal glands, combined with the low serum cortisol and clinical history, are essentially diagnostic of an adrenal crisis due to autoimmune adrenalitis. The cause of death was determined to be adrenal crisis in the setting of rotavirus gastroenteritis due to adrenal insufficiency (Addison disease).

DISCUSSION

Although timely diagnosis of adrenal insufficiency is needed to initiate treatment and prevent adrenal crisis, it is often delayed due to the nonspecific nature of the presenting symptoms. Initial symptoms and signs may include nausea and vomiting, behavioral changes, poor weight gain, hypoglycemia, weakness, and hypotension (1, 6). Further confounding the issue is the inconsistent presence of specific findings to suggest primary AI. Skin hyperpigmentation, often thought of

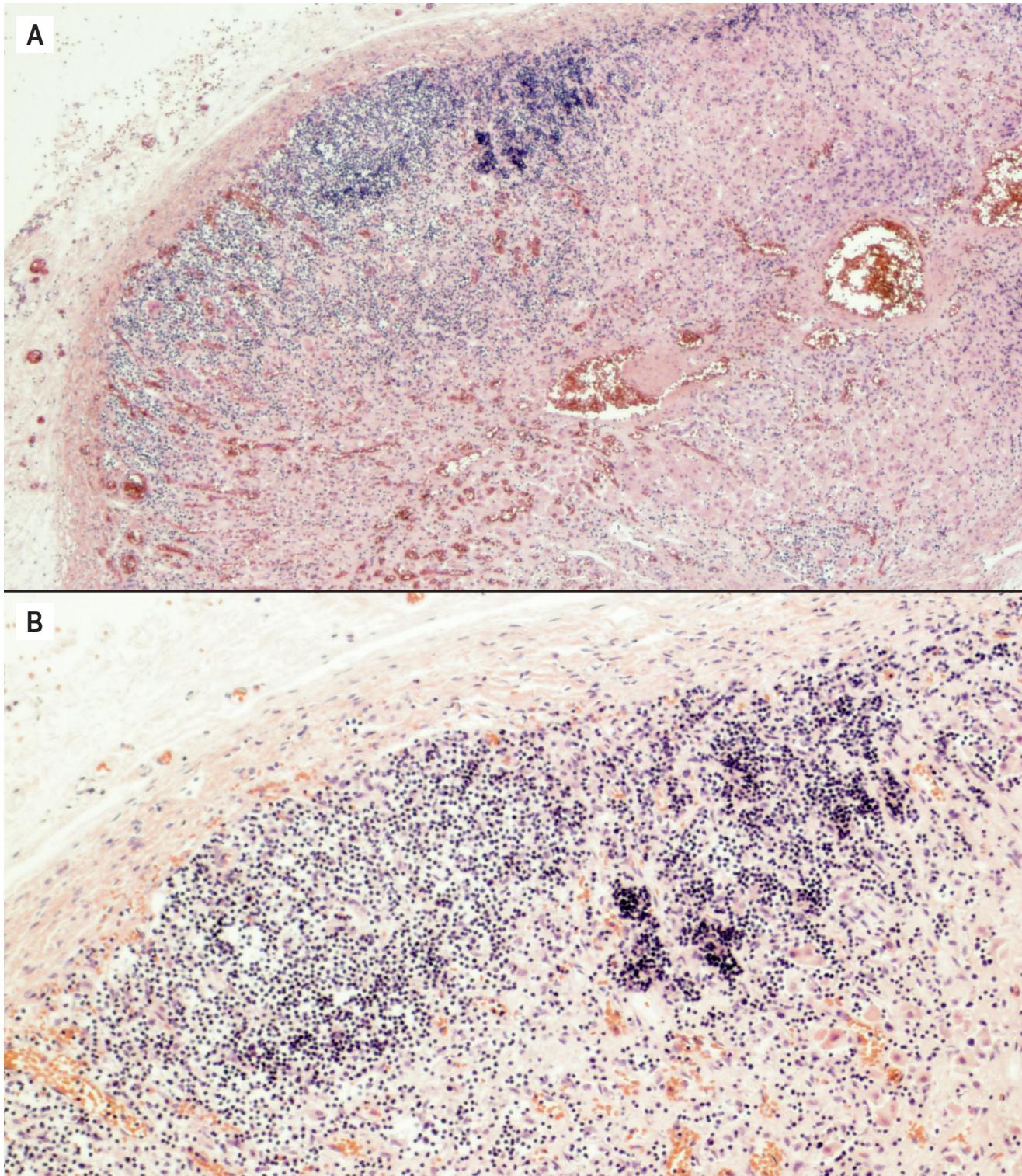


Image 1: Photomicrograph of the left adrenal gland demonstrating diffuse infiltration and destruction of the adrenal cortex by lymphocytes and plasma cells. **A)** H&E, x40 **B)** H&E, x100.

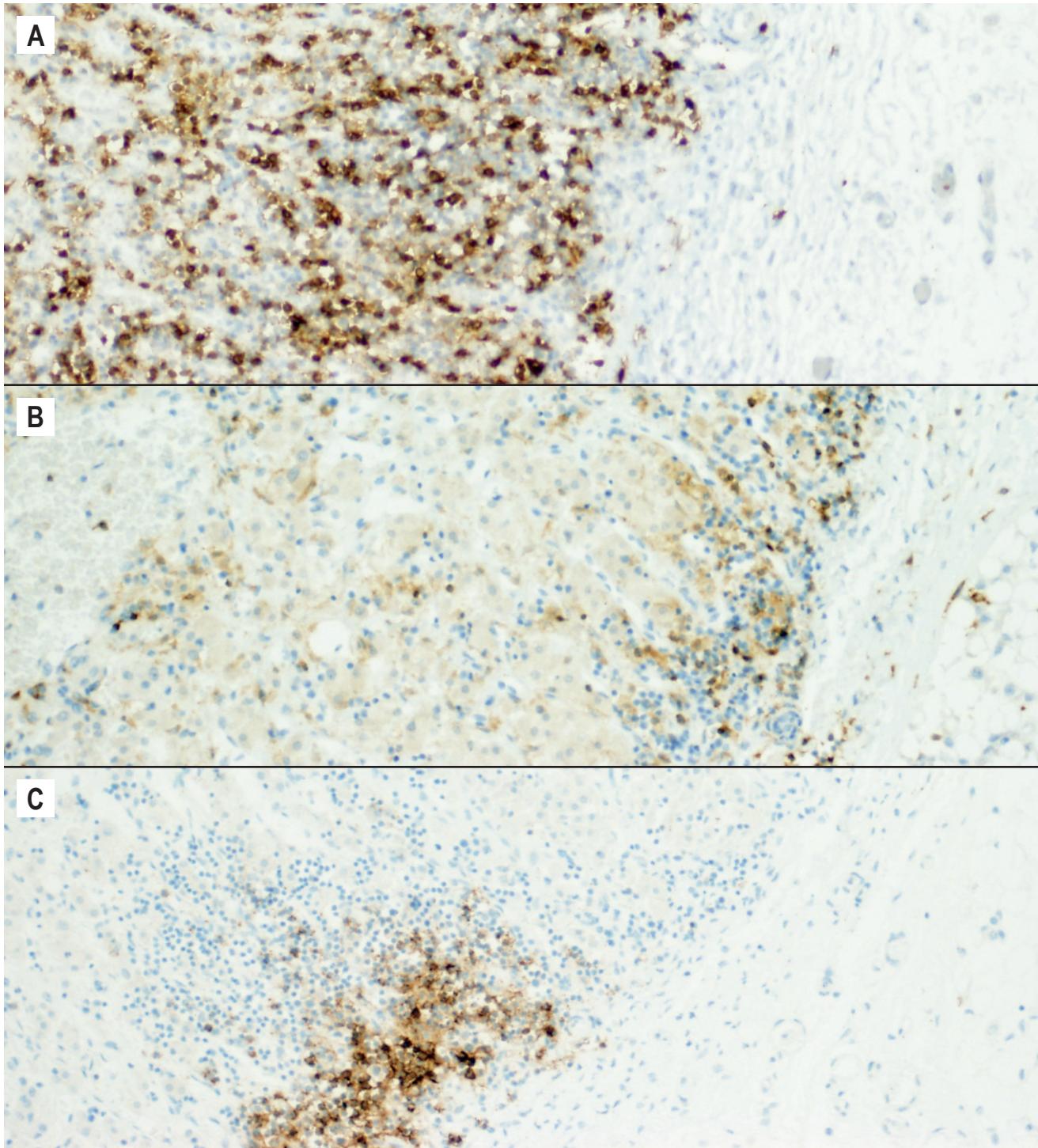


Image 2: Immunohistochemistry of left adrenal gland demonstrating proportion of CD8+ T cells, CD4+ T cells, and B cells. This series of photomicrographs depicts the results of immunohistochemical staining of the left adrenal glands for **A)** CD8 (x100), **B)**, CD4 (x100), and **C)** CD20 (x100). This demonstrates a slight predominance of CD8+ to CD4+ T cells, and highlights scattered follicle formation by B cells.



as a classic sign of primary AI, may be absent in up to one third of patients (and was absent in the presented case). Hyperkalemia is also absent in up to 50% of children and usually only mild when present (1, 7). One study that examined children with non-CAH primary AI found a delay in diagnosis of up to 0.5-5 years, and 25% of these children presented in frank adrenal crisis (8). Adrenal crises can also be precipitated by infection, as in the case presented here, surgery, or trauma, as these physiologic stresses increase demand for cortisol and the adrenal glands are unable to respond appropriately (2).

At autopsy, the adrenal glands in autoimmune AI can be normal-sized, atrophic, or nearly unidentifiable. Other common causes of primary AI in children include traumatic adrenal hemorrhage, adrenal hemorrhage due to infection (i.e., Waterhouse-Friderichsen Syndrome), thrombosis from antiphospholipid antibody syndrome, direct infection of the gland (e.g., tuberculosis), X-linked adrenoleukodystrophy, and other congenital syndromes (7, 13). However, these etiologies do not cause atrophy of the adrenals. Histologic exam of the adrenal cortex in autoimmune AI typically shows a lymphocyte-predominant infiltrate with associated follicle formation and fibrosis. In the late stages of disease, the glands may be predominantly fibrotic with only minimal inflammation (6, 9).

Postmortem laboratory studies supportive of primary AI include a depressed serum cortisol concentration, often <3 µg/dL. The cut-off for "low" cortisol may even be raised to 20 µg/dL in patients who are critically ill, and should be demonstrating elevated cortisol as a stress response. Clearly, there is room for uncertainty; some authors suggest a cutoff of <5 µg/dL to increase sensitivity, and additionally, cortisol concentrations are known to fluctuate during the day (2, 10). The concentrations measured, therefore, needs to be interpreted in the clinical context in order to understand its significance. Serum cortisol has been described to be stable at least up to 18-20 hours postmortem, and possibly up until the onset of recognizable decomposition (2, 10, 11). In the case presented, the postmortem interval between death and autopsy was only 18 hours, so this should not significantly

confound the interpretation of the decreased cortisol concentration.

While hyponatremia can be detected in the vitreous fluid seen due to loss of aldosterone, vitreous sodium does decrease with increasing decomposition and this must be considered. Hypoglycemia may be detected in the vitreous fluid as well, due to the loss of cortisol, but vitreous glucose is also known to drop after death and so a low value must be interpreted with some scrutiny. Evaluating hyperkalemia in vitreous fluid is entirely unreliable, as potassium begins to increase immediately and unpredictably after death. If antemortem samples are available for testing, then these electrolyte derangements could be confirmed (2, 12). Adrenocorticotropic hormone concentrations and plasma renin activity can also be measured on antemortem samples, and should both be elevated in primary AI (7). In the case presented, no antemortem samples were available for testing.

The detection of auto-antibodies against 21-hydroxylase is specific for autoimmune AI, and can be done on postmortem samples (2).

Other associated endocrinopathies need to be considered when investigating a potential case of autoimmune AI. Autoimmune AI can occur in children in isolation, or may be part of the Autoimmune polyglandular syndromes (types 1, 2, or 4). Autoimmune polyglandular syndromes Type 1 is defined by a germline mutation in the *AIRE-1* gene, and presents with adrenal insufficiency, hypoparathyroidism, and mucocutaneous candidiasis. Autoimmune polyglandular syndrome Type 2 has no single specific mutation, but is defined as adrenal insufficiency with immune-mediated diabetes mellitus and autoimmune thyroiditis. Type 4 is simply any constellation of autoimmune diseases that doesn't fit into the other categories (6). In this patient, there was no indication of other endocrinopathies or chronic *Candida* infections, although it is possible other autoimmune diseases may have developed, had she survived.

In the case presented, the low serum cortisol is very supportive of an adrenal crisis. Although 21-hydroxy-



lase antibodies were not tested in this case, the finding of atrophic adrenal glands with dense lymphoplasma-cytic infiltration is specific for autoimmune Addison Disease. It is likely that this child initially had sub-clinical AI; no skin hyperpigmentation was seen on exam, and she had been previously healthy (although her underweight status may have been partially due to AI). The clinical history and viral antigen testing suggest that a gastrointestinal rotavirus infection unmasked her disease, causing an adrenal crisis.

CONCLUSION

This case re-emphasizes that although adrenal insufficiency is a rare diagnosis in childhood, it must be suspected in cases of sudden death, particularly those with a preceding illnesses or surgery.

REFERENCES

- 1) Hsieh S, White PC. Presentation of primary adrenal insufficiency in childhood. *J Clin Endocrinol Metab.* 2011 Jun; 96(6):E925-8. PMID: 21470994. <https://dx.doi.org/10.1210/jc.2011-0015>.
- 2) Kemp WL, Koponen MA, Meyers SE. Addison Disease: the first presentation of the condition may be at autopsy. *Acad Forensic Pathol.* 2016 Jun; 6(2):249-57.
- 3) Shulman DI, Palmert MR, Kemp SF; Lawson Wilkins Drug and Therapeutics Committee. Adrenal insufficiency: still a cause of morbidity and death in childhood. *Pediatrics.* 2007 Feb; 119(2):e484-94. PMID: 17242136. <https://dx.doi.org/10.1542/peds.2006-1612>.
- 4) Levy-Shraga Y, Pinhas-Hamiel O. Novel insights into adrenal insufficiency in childhood. *Minerva Pediatr.* 2014 Dec; 66(6):517-32. PMID: 25058175.
- 5) Perry R, Kecha O, Paquette J, et al. Primary adrenal insufficiency in children: twenty years experience at the Sainte-Justine Hospital, Montreal. *J Clin Endocrinol Metab.* 2005 Jun; 90(6):3243-50. PMID: 15811934. <https://dx.doi.org/10.1210/jc.2004-0016>.
- 6) Ten S, New M, Maclare N. Clinical review 130: Addison's disease 2001. *J Clin Endocrinol Metab.* 2001 Jul; 86(7):2909-22. PMID: 11443143. <https://dx.doi.org/10.1210/jcem.86.7.7636>.
- 7) Caplan MJ. A practical forensic approach to fatal pediatric endocrinopathies. *Acad Forensic Pathol.* 2016 Jun; 6(2): 258-70.
- 8) Simm PJ, McDonnell CM, Zacharin MR. Primary adrenal insufficiency in childhood and adolescence: advances in diagnosis and management. *J Paediatr Child Health.* 2004 Nov; 40(11):596-9. PMID: 15469526. <https://dx.doi.org/10.1111/j.1440-1754.2004.00482.x>.
- 9) Betterle C, Morlin L. Autoimmune Addison's disease. *Endocr Dev.* 2011; 20:161-72. PMID: 21164269. <https://dx.doi.org/10.1159/000321239>.
- 10) Clapper A, Nashelsky M, Dailey M. Evaluation of serum cortisol in the postmortem diagnosis of acute adrenal insufficiency. *Am J Forensic Med Pathol.* 2008 Jun; 29(2):181-4. PMID: 18520491. <https://dx.doi.org/10.1097/PAF.0b013e318174e7c8>.
- 11) Finlayson NB. Blood cortisol in infants and adults: a postmortem study. *J Pediatr.* 1965 Feb; 67(2):248-52. [https://doi.org/10.1016/s0022-3476\(65\)80247-5](https://doi.org/10.1016/s0022-3476(65)80247-5).
- 12) Palmiere C, Mangin P. Postmortem chemistry update part I. *Int J Legal Med.* 2012 Mar; 126(2):187-98. PMID: 21947676. <https://dx.doi.org/10.1007/s00414-011-0625-y>.
- 13) Uçar A, Baş F, Saka N. Diagnosis and management of pediatric adrenal insufficiency. *World J Pediatr.* 2016 Aug; 12(3):261-74. PMID: 27059746. <https://dx.doi.org/10.1007/s12519-016-0018-x>.



A Case of Previously Unsuspected Huntington Disease Diagnosed at Autopsy

Catherine R. Miller, Nobby C. Mambo, Jianli Dong, Gerald A. Campbell

ABSTRACT

Huntington disease (HD) is a neurodegenerative disorder with a worldwide prevalence of four to ten per 100 000. It is characterized by choreiform movements, behavioral/psychiatric disturbances, and eventual cognitive decline. Symptoms usually present between 30 and 50 years of age and the diagnosis is based on the combination of clinical symptoms, family history, and genetic testing. A variation of HD, juvenile Huntington disease (JHD), presents earlier, with more severe symptoms and with a worse prognosis. Symptoms are different in JHD, with personality changes and learning difficulties being the predominant presenting features. Seizures are common in JHD, and chorea is uncommon; movement disorders at presentation of JHD are predominantly nonchoreiform. The inheritance pattern for both HD and JHD is autosomal dominant and the disease is caused by an elongation of the CAG repeat in the huntingtin gene.

There are many published case reports of Huntington disease that were confirmed at autopsy, but to our knowledge, there are no reports in the literature where the diagnosis of Huntington disease was first made at autopsy. We present a case of a 28-year-old African-American male who was in a state of neglect due to a lifetime of abuse, cognitive difficulties, and seizures, whose cause of death was pneumonia.

The gross autopsy findings included bilateral caudate nucleus atrophy and lateral ventricular dilation. Microscopically, severe bilateral neuronal loss and gliosis of the caudate and putamen nuclei were seen. Genetic testing for the number of CAG repeats confirmed the diagnosis and was consistent with JHD. *Acad Forensic Pathol.* 2017 7(1): 136-144

AUTHORS

Catherine R. Miller MD, University of Texas Medical Branch at Galveston - Pathology

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

Nobby C. Mambo MD, Galveston Medical Examiner's Office - Pathology

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

Jianli Dong MD PhD, University of Texas Medical Branch at Galveston - Pathology

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, writing assistance and/or technical editing.

Gerald A. Campbell MD PhD, University of Texas Medical Branch at Galveston - Pathology

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, general administrative support, writing assistance and/or technical editing.

CORRESPONDENCE

Catherine R. Miller MD, 301 University Blvd., Galveston TX 77555, catmille@utmb.edu

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

This work was presented at the 2016 NAME Annual Meeting. The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Autopsy, Neuropathology, Huntington disease, Juvenile Huntington disease, Molecular diagnostics

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2017 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2017.016>

Submitted for consideration on 18 Sep 2016. Accepted for publication on 20 Dec 2016



INTRODUCTION

Huntington disease (HD) is a progressive and fatal neurodegenerative disorder with a worldwide prevalence of four to ten per 100 000 persons and regional variations in prevalence, making it the most common single-gene neurodegenerative disorder (1-5). It is characterized by choreiform movements, behavioral/psychiatric disturbances, and eventual mental decline (2, 6). Symptoms usually present between the ages of 30 and 50 years, with death occurring within 15 to 20 years after the onset of symptoms (2).

The clinical diagnosis is made based on the combination of symptoms, family history, and genetic testing, and characteristic lesions (early striatal atrophy, particularly of the caudate nucleus, and potential cortical and/or cerebellar atrophy late in the course of the disease) may be detected while the patient is still living or at autopsy using magnetic resonance imaging (7-9). Classic pathologic findings at autopsy include lateral ventricle dilation and bilateral caudate atrophy; in severe cases, the atrophy may extend to the rest of the basal ganglia structures (3, 4).

The inheritance pattern is autosomal dominant with anticipation. The disease is caused by an elongation of the cytosine-adenine-guanine (CAG) repeat in the huntingtin gene (IT-15; "Interesting transcript 15") (5, 8). The locus of the CAG repeat in the huntingtin gene is on exon 1 and the gene itself is located on chromosome 4p16.3. The range of repeats in normal alleles is 6-26, with the most common allele lengths containing 17 and 19 repeats (5, 8). A definitive diagnosis of Huntington disease can be made in any patient with a repeat length equal to or greater than 40. The intermediate-ranges of 27-35 and 36-39 are considered to be the mutable normal allele range and the reduced penetrance range, respectively, and a repeat length of greater than 50-60 may be diagnostic of Juvenile HD (JHD) (2, 5, 8). It is thought that the huntingtin gene functions as a housekeeping gene, and that the mutation associated with increased repeats is a gain of function mutation. The result is increased production of the mutated, truncated huntingtin protein, which is insoluble and creates interfering, multimerized aggre-

gates inside the nuclei of the neocortical, neostriatal, and dentate neurons of Huntington patients, which may only be detected using immunohistochemical stains (2, 8).

Juvenile Huntington disease is a variation of classic HD that shows onset of symptoms in the first or second decade of life (10-12). It is thought that the worldwide prevalence of JHD is 4-9%, and that 5-10% of all HD sufferers are afflicted with JHD (10, 11). In 90% of JHD cases, the affected parent is the father (10). Classic HD is typically seen in adults, and JHD may not even be on the radar of a pediatrician evaluating a child for developmental delays or other symptoms. The rarity of the disease makes the diagnosis more challenging, and this is compounded by the fact that the presenting symptoms of JHD are dissimilar to the symptoms typically seen in classic HD. Juvenile Huntington disease typically presents with seizures (with which psychotic episodes may be associated) and early behavioral, cognitive, and speech/language problems manifesting as problems at school (indeed, these may be the presenting symptoms). Rigidity, dystonia, and bradykinesia are all more common movement disorders in this population than the choreiform movements seen in classic HD (10-13).

There are many published case reports of diagnoses of Huntington disease confirmed at autopsy in the literature, but to our knowledge there are no reports in the same literature where the diagnoses of Huntington disease was made initially at autopsy (1, 3-5, 7).

CASE REPORT

A 28-year-old male with a past medical history of cognitive difficulties and seizures, who was in a state of neglect due to a lifetime of abuse at the hands of his mother and her boyfriend, died of pneumonia. The patient was a ward of the state of Texas, and the whereabouts of his mother and biological father are unknown. The details of the patient's past medical history are not known.

The decedent was autopsied by the local medical examiner using standard autopsy procedures.

The brain and spinal cord were submitted for consultation to the autopsy service at our institution based on the medical examiner's concerns regarding the decedent's history of seizure and developmental delays.

The brain and spinal cord were fixed for two weeks in 20% formalin; gross and microscopic evaluations were performed on the brain, and only gross evaluation was performed on the spinal cord. The brain and spinal cord were examined by one of our institution's neuropathologists (GAC). The cerebrum was coronally sectioned at approximately 1.0 cm thickness per section after visually evaluating the cerebral vessels for atherosclerotic plaques and separating the cerebellum and brainstem from the cerebrum. The cerebellum was sectioned sagittally at approximately 0.5 cm thickness per section and the brainstem was transversely sectioned at approximately 0.5 cm thickness per section.

The following sections were submitted for histologic evaluation: frontal lobe (area 8), basal ganglia, hippocampus, thalamus, substantia nigra, cerebellum, and basilar artery. All sections are part of the standard neuropathology technique at our institution, with the exception of the thalamus, substantia nigra, and basilar artery. All slides were stained with hematoxylin and eosin (H&E) and Luxol fast blue/H&E (LFB/H&E). Sections of the hippocampus and basal ganglia were also stained with glial fibrillary acidic protein (GFAP), the basilar artery slide was additionally stained with pancytokeratin (AE1/3 monoclonal antibody cocktail) and epithelial membrane antigen (EMA), and both the hippocampus and basilar artery slides were additionally stained with periodic acid-Schiff (PAS). Additional staining for HD (e.g., ubiquitin, mutant-huntingtin protein) was not performed due to lack of stain availability, contrasted with availability and relative ease of genetic testing at our institution.

Blood cards obtained from the medical examiner's office were subjected to genetic testing. Capillary electrophoresis on an agarose gel method was used as a screening test for the patient's HD status. Confirmatory testing was performed using polymerase chain reaction (PCR) amplification with the GeneAmp 9700

Thermal Reaction Cycler (Thermo Fisher Scientific, Waltham, MA), and the results were analyzed using the GeneMapper Software 5 (Thermo Fisher Scientific, Waltham, MA) (13-15).

The gross autopsy findings were characteristic of HD and related neurodegenerative disorders (9, 16, 17). The brain weighed 1270 g (our institution's normal male brain weight range is 1200 – 1400 g). The cerebral gyri did not appear grossly atrophic. Coronal sectioning revealed moderate dilation of the cerebral ventricles bilaterally, and marked bilateral atrophy with flattening of the ventricular surfaces of the heads of the caudate nuclei as compared to a comparison (non-age-matched) normal brain (**Images 1 and 2**). The putamen and globus pallidus appeared grossly normal. The laminations of the hippocampi bilaterally were accentuated, raising the question of ischemia or atrophy, although microscopically there was no evidence of either ischemia or atrophy. Additionally, the hippocampi were neither grossly nor microscopically sclerotic, despite the patient's reported history of seizures. Microscopically, there was severe bilateral neuronal loss and marked reactive gliosis (increase in the number and size of astrocytes, and increase in the number of oligodendrocytes and rod-shaped microglial cells demonstrated by GFAP immunohistochemical stain of the corpus striatum (caudate and putamen nuclei [**Images 3, 4, and 5**]), corresponding to Vonsattel's grade 3 HD. Possible grades for a given brain using the Vonsattel grading system are 0, 1, 2, 3, and 4, and are based on both macroscopic and microscopic observations, in increasing order of disease severity; the Vonsattel grade closely corresponds to the extent of clinically observed disability (3, 4). The neocortical gray matter and other deep nuclei, including the globus pallidus, were less severely affected, which prevented a categorization of this disease process into Vonsattel's grade 4. The cerebral myelinated white matter was not significantly reduced, based on LFB staining. An incidental finding of a small, firm, thin, white-to-translucent plaque present in the leptomeninges on the ventral surface of the rostral basilar artery was also noted, and was diagnosed as a benign notochordal hamartoma (echordosis physilaphora). No evidence of recent or

remote trauma was identified, despite the patient's reported history of abuse.

No gross or microscopic evidence of the reported history of abuse was noted in the brain or spinal cord, and the cerebellum, brain stem, and spinal cord were all grossly and microscopically without pathologic change.

Capillary electrophoresis confirmed that there was one expanded huntingtin allele and one normal allele present in this patient (18). The confirmatory PCR amplification testing also allowed for CAG repeat quantitation. The patient exhibited 19 repeats on his nonmutated allele and 64 repeats on his mutated allele, confirming the diagnosis of Huntington disease (**Figure 1**). Given the number of repeats and the early reported age (exact age unknown) or symptom onset, the authors are comfortable not only diagnosing the patient with HD, but further completing the diagnosis with a diagnosis of JHD.



Image 1: Frontal coronal slice showing severe symmetric atrophy of the caudate nuclei. The putamen nuclei are grossly normal.

DISCUSSION

Huntington disease is a rare, progressive, and fatal neurodegenerative disorder. There have been several cases of suspected HD reported in the literature that have been confirmed at autopsy, but to our knowledge, the case we present here is the first where the patient was initially diagnosed with HD at autopsy. Our decedent, a 28-year-old African-American male with a history of cognitive difficulties, seizure disorder, and physical abuse, was especially young for the onset of HD. This early onset possibly led to the failure of this diagnosis to be considered during his life. Very little is known about the patient's childhood, the status of the reported abuse, the circumstances that led to him being placed as a ward of the State of Texas, or the circumstances surrounding his death.

Although the worldwide prevalence of HD is estimated at four to ten cases per 100 000 persons, the majority of those cases occur in the Caucasian population

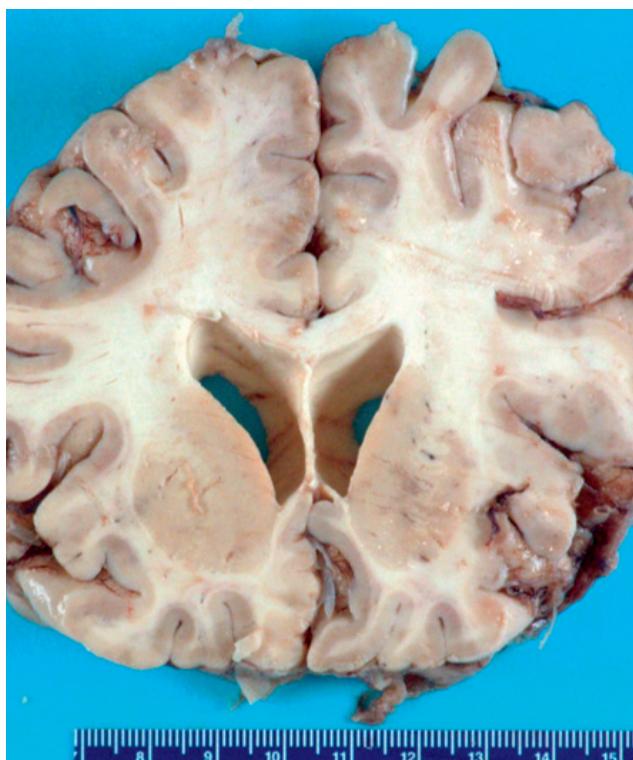


Image 2: Frontal coronal slice at a comparable level in a normal brain to illustrate normal caudate configuration.

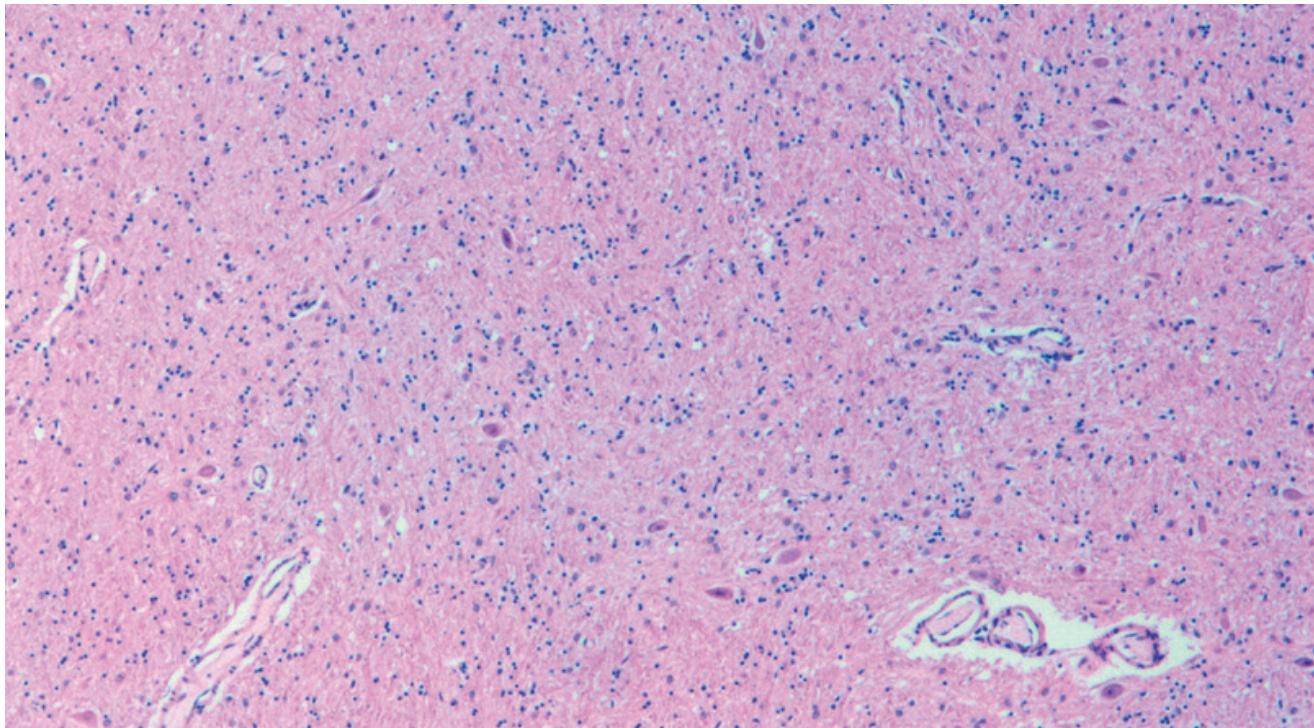


Image 3: Corpus striatum of patient showing few neurons and increased glial cells (H&E, x40).

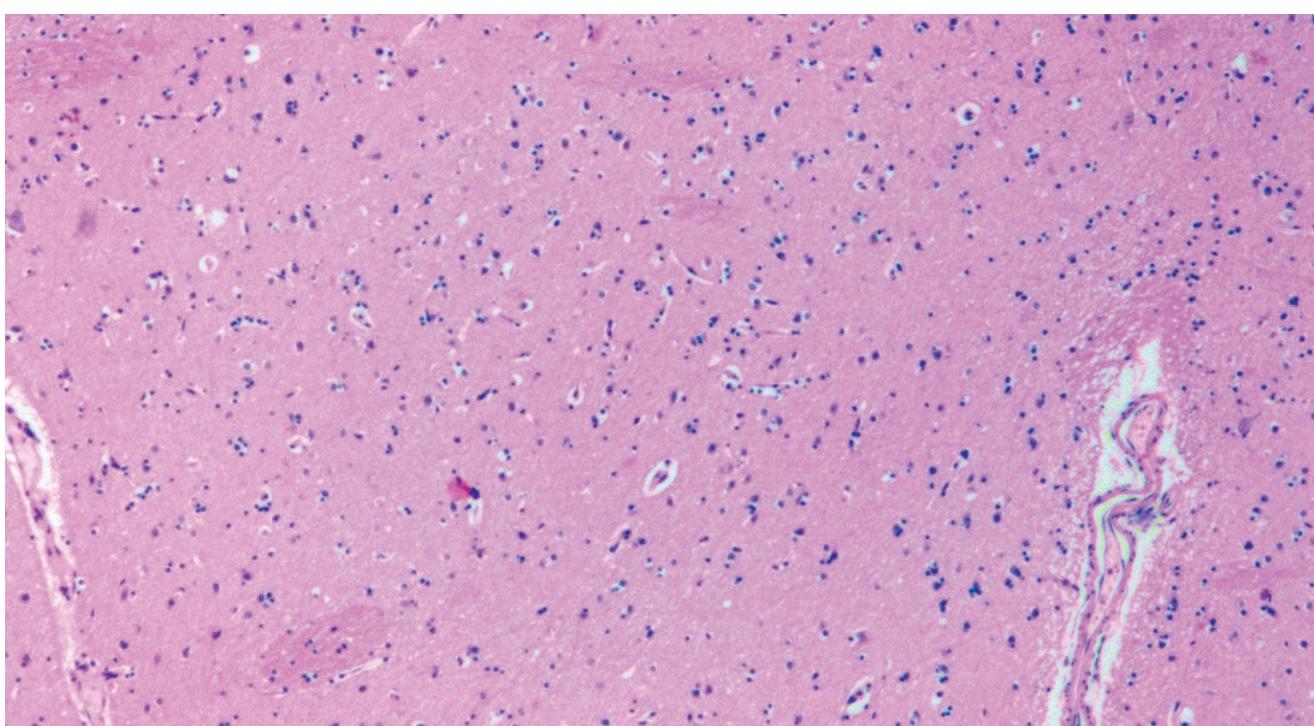


Image 4: Comparison normal corpus striatum (H&E, x40).

(1-5). It is thought that the prevalence of HD in the black or African-American population is considerably lower, on the order of 0.97 cases per 100 000 persons (19). The patient's cause of death was pneumonia, which is the most common cause of death in HD (1, 6, 20). Of course, other causes of death in HD, such as choking and suicidal causes, are also common, and may also be encountered in the forensic setting (6).

At autopsy, the caudate nuclei were grossly atrophic bilaterally, with associated moderate lateral ventricular dilation. Microscopy showed severe bilaterally symmetric caudate and putamen atrophy with marked reactive astrocytosis (gliosis), corresponding to Von-sattel's grade 3 HD (3, 4). The globus pallidus and nucleus accumbens were significantly less affected in our patient, which excluded advancement of the grade to 4. No neuronal inclusions were identified (although specific staining was not done), and there was not a significant loss of myelinated cerebral white matter, despite the enlargement of the lateral ventricles (en-

largement was therefore likely due mainly to atrophy of the corpus striatum). Frontoparietal cortical atrophy was also not identified in this case, although it has been shown that the degree of cortical atrophy in HD patients correlates with the number of CAG repeats, and may be more severe in later stages of the disease (21). The cerebellum, brain stem, and spinal cord were all without pathologic change. It also is worth noting that though HD-specific staining (i.e., ubiquitin, mutant huntingtin protein) was not performed before performing genetic testing on this patient due to lack of stain availability at our institution, at an institution where these stains are readily available, performing them would be a reasonable step between evaluation of H&E-stained slides and performance of genetic testing.

Though the gross and microscopic findings of the patient's brain at autopsy led to the suspicion of HD, the patient's clinical picture was complicated by his cognitive impairment, seizures, and a history of phys-

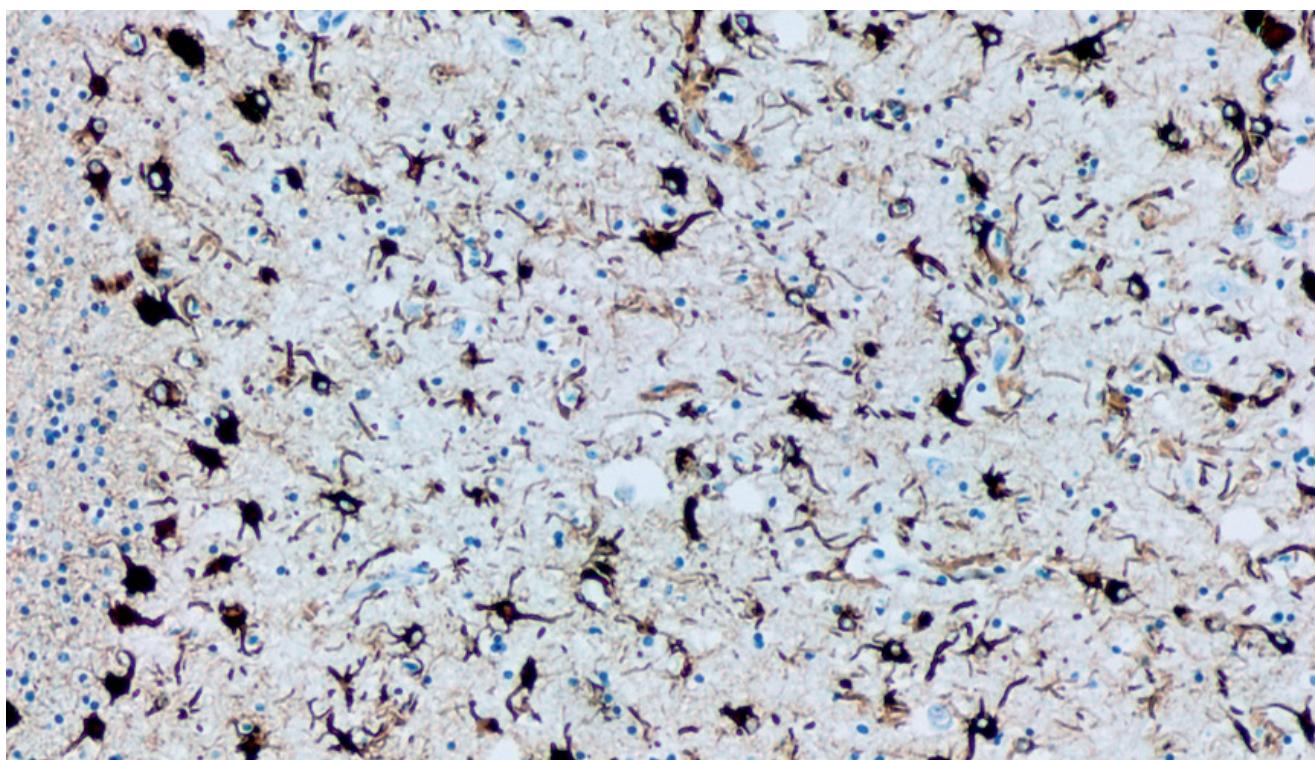


Image 5: Corpus striatum of the patient showing severe reactive astrocytosis (GFAP, x100).

ical abuse. The patient's cognitive impairment could have been the result or the cause of the physical abuse the patient reportedly suffered as a child. However, cognitive impairment and seizures (from which the patient also suffered) are common presenting and often predominant symptoms in JHD. These symptoms, with the added factors of an abusive home life, the patient's young age, and the patient's race are all circumstances, which when taken in combination, would have made the diagnosis of JHD extremely difficult for a treating physician.

Additionally, the patient's general picture of cognitive impairment and seizures, coupled with the findings of bilateral caudate and putamen atrophy, provides a postmortem differential for the diagnosis of other neurodegenerative disorders that affect the basal ganglia. These disorders include but are not limited to chorea-acanthocytosis, McLeod syndrome, Huntington disease-like 1, 2, and 3 (HDL1, HDL2, HDL3), multiple system atrophy (MSA), and pantothenate

kinase-associated neurodegeneration (PKAN). They may be inherited in an autosomal dominant (as in HD), X-linked (McLeod syndrome), or autosomal recessive (chorea-acanthocytosis) pattern, with some diseases in this category showing unusual inheritance patterns, potential founder effects, and potential ubiquitin-positive intranuclear staining due to their natures as tripeptide repeat diseases (e.g., HLD2). These diseases are not trinucleotide repeat disorders, but instead are each caused by specific mutated genes on a variety of chromosomes (9, 16, 17). These diseases, although they should be considered by any evaluating neuropathologist presented with a case such as ours, are exceedingly rare. The evaluating neuropathologist may not wish to pursue them as a line of inquiry until genetic testing has effectively ruled out the more common diagnosis of HD or JHD.

As stated previously, the brain findings at autopsy led to the suspicion of HD and genetic testing confirmed the diagnosis.



Figure 1: Electropherogram result of the patient sample showing peaks at the normal (19 repeats) and affected (64 repeats) alleles. The screening electropherogram shows allele binning of stutter peaks generated from polymerase chain reaction amplicons using genomic DNA extracted from the patient sample. The vertical lines (y-axis) represent stutter peaks within each of the specific CAG bins separating along the horizontal line (x-axis) starting from the fifth CAG repeat as described (15). CAG repeats of normal, mutable, reduced penetrance allele, and affected alleles are marked at the top of the screen. The prominent peaks of the patient sample, located in the center of the stutter pattern, correspond to allele sizes of 19 and 64 repeats.

CONCLUSION

Huntington disease is inherited via an autosomal dominant mechanism, is considered to be fully penetrant at CAG repeat lengths greater than 40, and shows anticipation. Our patient was heterozygous for the huntingtin gene mutation, and his mutated allele showed a repeat length of 64. Repeat lengths of greater than 60 show increased likelihood of early onset of symptoms of HD (juvenile Huntington disease), which is likely what happened in this patient. Almost nothing is known about the patient's family, but from the results of our testing, it is highly likely that one of the patient's parents (most likely the father, as 90% of JHD cases are inherited via paternal meiotic instability) is likewise affected (10).

This case illustrates the importance of having good clinical and family information available at the time of autopsy and also the importance of an open mind and thorough examination in each autopsy performed. The autopsy pathologist must always be cognizant of the potential for an unexpected discovery of a neurodegenerative disorder, and must be willing to seek the help of a knowledgeable neuropathologist when confronted with a case that is suspicious. The ability to perform postmortem genetic testing on patients with potential neurodegenerative disorders is paramount to diagnosis, and may be of crucial importance to the family of the deceased. Huntington disease, in particular, is seen as a death sentence by many of its sufferers and proper diagnosis or confirmation of the disease in a decedent at autopsy is critical for family members when deciding to be tested themselves.

REFERENCES

- 1) Jauhar S, Ritchie S. Psychiatric and behavioural manifestations of Huntington's disease *Adv Psychiatr Treat*. 2010 Apr; 16(3):168-75. <https://doi.org/10.1192/apt.bp.107.005371>.
- 2) Margolis RL. Diagnosis of Huntington Disease. *Clin Chem*. 2003 Oct; 49(10):1726-32. PMID: 14500613. <https://doi.org/10.1373/49.10.1726>.
- 3) Vonsattel JP, Myers RH, Stevens TJ, et al. Neuropathological classification of Huntington's disease. *J Neuropathol Exp Neurol*. 1985 Nov; 44(6):559-77. PMID: 2932539.
- 4) Waldvogel HJ, Kim EH, Tippett LJ, et al. The neuropathology of Huntington's Disease. *Curr Top Behav Neurosci*. 2015;22:33-80. PMID: 25300927. https://dx.doi.org/10.1007/7854_2014_354.
- 5) Kawakami I, Katsuse O, Aoki A, et al. Autopsy case of concurrent Huntington's disease and neurofibromatosis type 1. *Psychogeriatrics*. 2014 Mar; 14(1):81-6. PMID: 24528652. <https://doi.org/10.1111/psyg.12040>.
- 6) Heemskerk AW, Roos RA. Aspiration pneumonia and death in Huntington's disease. Version 2. *PLoS Curr*. 2012 Jan 30 [revised 2012 Feb 2]; 4:RRN1293. PMID: 22307361. PMCID: PMC3269785. <https://dx.doi.org/10.1371/currents.RRN1293>.
- 7) Kenney C, Powell S, Jankovic J. Autopsy-proven Huntington's disease with 29 trinucleotide repeats. *Mov Disord*. 2007 Jan; 22(1): 127-30. PMID: 17115386. <https://dx.doi.org/10.1002/mds.21195>.
- 8) Bean L, Bayrak-Toydemir P. American College of Medical Genetics and Genomics standards and guidelines for clinical genetics laboratories, 2014 edition: technical standards and guidelines for Huntington disease. *Genet Med*. 2014 Dec; 16(12):e2. PMID: 25356969. <https://dx.doi.org/10.1038/gim.2014.146>.
- 9) Martino D, Stamelou M, Bhatia KP. The differential diagnosis of Huntington's disease-like syndromes: 'red flags' for the clinician. *J Neurol Neurosurg Psychiatry*. 2013 Jun; 84(6):650-6. PMID: 22993450. PMCID: PMC3646286. <https://dx.doi.org/10.1136/jnnp-2012-302532>.
- 10) Nance MA, Mathias-Hagen V, Breningstall G, et al. Analysis of a very large trinucleotide repeat in a patient with juvenile Huntington's disease. *Neurology*. 1999 Jan 15; 52(2):392-4. PMID: 9932964. <https://doi.org/10.1212/wnl.52.2.392>.
- 11) Patra KC, Shirodkar MS. Childhood-onset (juvenile) Huntington's disease: a rare case report. *J Pediatr Neurosci*. 2015 Jul-Sep; 10(3): 276-9. PMID: 26557176. PMCID: PMC4611904. <https://dx.doi.org/10.4103/1817-1745.165709>.
- 12) Quarrell OW, Nance MA, Nopoulos P, et al. Managing juvenile Huntington's disease. *Neurodegener Dis Manag*. 2013 Jun 1; 3(3). PMID: 24416077. PMCID: PMC3883192. <https://dx.doi.org/10.2217/nmt.13.18>.
- 13) Reyes Molón L, Yáñez Sáez RM, López-Ibor Alcocer MI. Juvenile Huntington's disease: a case report and literature review. *Actas Esp Psiquiatr*. 2010 Sep-Oct; 38(5):285-94. English, Spanish. PMID: 21117003.
- 14) Lee Y, Oh MR, Kim CH, et al. A simple method for the detection of neurologic disorders associated with CAG repeat expansion using PCR-microtiter plate hybridization. *J Biotechnol*. 2002 May 23; 95(3):215-23. PMID: 12007862. [https://doi.org/10.1016/s0168-1656\(02\)00024-x](https://doi.org/10.1016/s0168-1656(02)00024-x).
- 15) Jama M, Millson A, Miller CE, Lyon E. Triplet repeat primed PCR simplifies testing for Huntington disease. *J Mol Diagn*. 2013 Mar; 15(2):255-62. PMID: 23414820. <https://dx.doi.org/10.1016/j.jmoldx.2012.09.005>.
- 16) Peall KJ, Kurian MA. Benign hereditary chorea: an update. *Tremor Other Hyperkinet Mov (N Y)*. 2015 Jul 14; 5:314. PMID: 26196025. PMCID: PMC4502401. <https://dx.doi.org/10.7916/D8RJ4HM5>.
- 17) Walker RH, Saiki S, Danek A. Neuroacanthocytosis syndromes II. Berlin: Springer; 2007. 295 p.
- 18) Blanco S, Suarez A, Gandia-Pla S, et al. Use of capillary electrophoresis for accurate determination of CAG repeats causing Huntington disease. An oligonucleotide design avoiding shadow bands. *Scand J Clin Lab Invest*. 2008; 68(7):577-84. PMID: 19378429. <https://dx.doi.org/10.1080/00365510801915171>.
- 19) Wright HH, Still CN, Abramson RK. Huntington's disease in black kindreds in South Carolina. *Arch Neurol*. 1981 Jul; 38(7):412-4. PMID: 6454404. <https://doi.org/10.1001/archneur.1981.00510070046005>.



CASE OF THE MONTH

AFP

- 20) Sørensen SA, Fenger K. Causes of death in patients with Huntington's disease and in unaffected first degree relatives. *J Med Genet.* 1992 Dec; 29(12):911-4. PMID: 1479606.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1016212/>.
- 21) Halliday GM, McRitchie DA, Macdonald V, et al. Regional specificity of brain atrophy in Huntington's disease. *Exp Neurol.* 1998 Dec; 154(2):663-72. PMID: 9878201.
<https://dx.doi.org/10.1006/exnr.1998.6919>.

Page 144

Miller et al. • Huntington at Autopsy

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS
©2017 Academic Forensic Pathology International

Downloaded from www.afpjurnal.com by an AFP Journal subscriber
This article is for personal use only and may not be shared or distributed in any fashion