False-Positive Rate for Suspected Drug-Related Deaths Following Full Autopsy

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Abstract: The sharp increase in drug-related deaths has tempted medical examiner/coroner offices to perform external examinations with comprehensive toxicology testing instead of performing a standard autopsy. Compounding the problem of an increasing workload has been the decrease in available forensic pathologists. Opting for external examinations on suspected drug-related fatalities, however, is antithetical to current best practices. The purpose of this study was to review case files, autopsy reports, and toxicologic results of all deaths that were autopsied at the authors' facility and decide whether significant disease processes or injuries that would supersede the results of toxicologic testing and external examination findings alone were being missed.

Key Words: overdose deaths, forensic pathology, autopsy practice

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Drug-related fatalities in the United States have risen steadily since the late 1990s with a sharp increase of deaths in 2016 onward driven by opioid use specifically with fentanyl and its analogs and stimulant use such as methamphetamine and cocaine.[1–11] This drastic increase in drug-related fatalities is reflected both within the authors' region of western North Carolina and on a national level (Fig. 1). In 2021 alone, more than 100,000 drug-related fatalities occurred nationally, of which greater than 70,000 of those deaths involved synthetic opioids.[12]

As the number of drug-related fatalities drastically increases, so does the demand for the performance of standard autopsies as this is the current best practice per the National Association of Medical Examiners as of August 2023.[13,14] This increase in demand has prompted intense discussion at national conferences such as the National Association of medical examiners conference regarding the possibility of medical examiner/coroner offices who have been performing standard autopsies on suspected drug-related deaths to perform external examinations and obtaining toxicologic specimens instead of a standard autopsy when scene investigation strongly indicates a drug-related fatality performance of a standard autopsy.[15]

The Atrium Health Wake Forest Baptist Regional Autopsy Center (AHWFBRAC), which provides medicolegal autopsy service for 33 counties in western North Carolina with a total population of 2,354,038, performed standard autopsies on suspected drug-related fatalities through 2021 even when other medical examiner/coroner offices had adopted the performance of external viewings and acquisition of toxicology specimens. As a result, the investigators had the ability, through retrospective analysis of the autopsy and toxicologic findings for suspected drug-related deaths, to determine whether the performance of an external examination and comprehensive toxicological analysis alone missed significant disease processes or injuries that would change the cause of death in suspected drug-related fatalities.

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METHODS/MATERIALS

The authors at AHWFBRAC reviewed information from files in which a standard medicolegal autopsy had been performed at AHWFBRAC between the years 2016 and 2021. Decedents less than 18 years of age, deaths from obvious lethal injury, and deaths from intentional suicidal prescription or illicit drug overdose were excluded from this study. Intentional drug overdose cases were excluded from this study for two reasons. First, these cases were already identified as intentional overdoses at the time of referral, introducing internal bias in categorizing them as true positives. Second, many of these cases did not meet the criteria for a likely drug-related death, as evidenced by instances where individuals without a history of substance use disorder or suicidal ideation attempted overdose without conclusive evidence of drugs at the scene. In such cases lacking a specific note indicating the intentional act of seeking death, accurate categorization based on the criteria used in this study was challenging and would ultimately lead to a standard autopsy to rule out anatomical causes of death.

Information extracted from the case files included age, sex, investigative information of the death scene, the preliminary report of death, the autopsy report, and the toxicology report. The preliminary report of death is a brief report available at the time of autopsy that summarizes information such as decedent's name and age, the date and time of death, as well as relevant information about the circumstances surrounding the decedents death and events leading up to the event of death like any trauma or recent illness. This report is often not all inclusive and additional information may be provided as further investigation is conducted. This information is obtained from the medicolegal death investigators at the regional autopsy center who obtain specific information regarding drug-related deaths from the county medical examiners using the same standardized questions the authors used in this study to assess for preliminary risk of a drug-related fatality.

The criteria used to make the determination of a likely drug-related fatality included the following investigative information: presence or absence of drug paraphernalia at the scene, current or prior history of a substance use disorder, and history of prior overdoses. Items that qualify as drug paraphernalia include but are not limited to the following: needles, syringes, cut straws, pill crushers, burnt aluminum foil, rolled papers, plastic baggies with residue, etc. Types of injuries and disease processes found postmortem and types of substances in blood or other tissues were tabulated from review of autopsy and toxicologic reports. The authors' purpose was to utilize this information to determine the false-positive and false-negative rates for suspected drug-related deaths.

Point-of-care qualitative urine drug screens, of which most use monoclonal antibodies in a lateral flow chromatographic immunoassay, were not used for this study. Specimens were submitted to

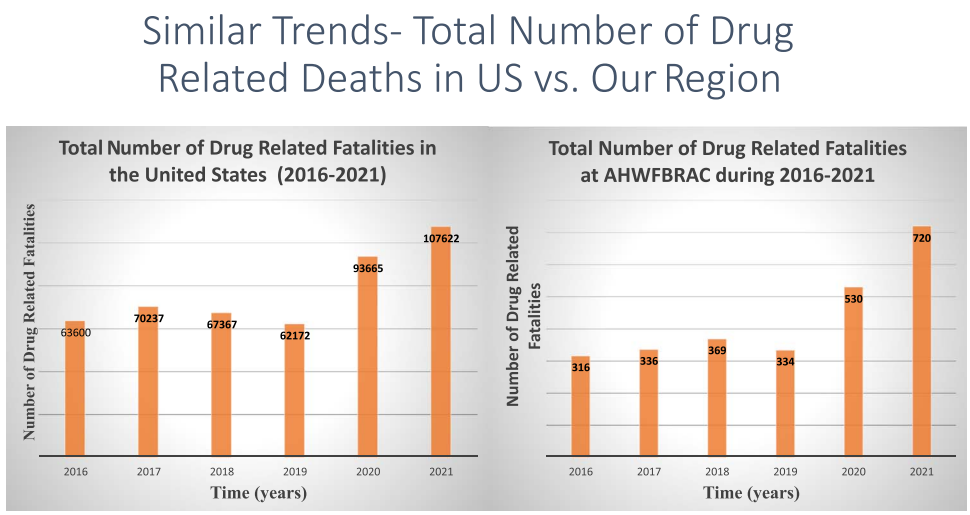

FIGURE 1. A comparison of similar trends in the total number of drug-related fatalities on a national level versus our region in western North Carolina over the same consecutive 6-year period.

a forensic toxicology laboratory that routinely screened for over-the-counter, prescription, and illicit drugs using an organic base/neutral extraction with an Agilent gas chromatography-mass spectrometer and an Agilent gas chromatograph-nitrogen phosphorus detector (GC-NPD) along with a targeted liquid chromatography-mass spectrometry method utilizing Thermo Scientific Q Exactive Focus hybrid quadrupole-Orbitrap mass spectrometer. Analytes detected by screening methodology were confirmed and quantitated using liquid chromatography-tandem mass spectrometry (LC-MS-MS).[16]

For this study, a false positive (FP) is defined as a case with a high suspicion of being a drug-related fatality upon referral as determined by investigative information and scene findings, but toxicological analysis was negative or in cases where there were illicit substances present within the decedents system but other significant non-toxicologic findings to explain the death were present. Similarly, a false negative (FN) is defined as a case with a very low or suspicion of drug involvement upon referral as determined by investigative information and scene findings, but toxicologic analysis determined a drug toxicity to be the cause of death in the absence of significant findings at autopsy. It is important to understand the definition of a false-positive rate and a false-negative rate is not universal. In this study, we are determining the false-positive rate to be defined as the proportion of positive preliminary results that are true negative over dose deaths and the false-negative rate to be defined as the proportion of negative preliminary findings that are true-positive overdose deaths. Utilizing these definitions when selecting cases and gathering data, the authors then used the tabulated data to calculate the following values: false-positive rate = (FP/total no. of suspected drug overdose cases); false-negative rate = (FN/total no. of toxicological confirmed overdose cases); sensitivity = (TP/TP + FN); specificity = (TN/TN + FP). An analysis was performed on the most common drug-related trends involved in these drug-related fatalities during the study period.

RESULTS

Our observations were tabulated, and a statistical analysis was performed on the data. Between 2016 and 2021, a total of 6248 autopsy case files were reviewed of which 2956 met the previously stated inclusion criteria with 2569 cases that were originally suspected to be drug-related fatalities at the time of referral, and 387 cases had no suspicion of having a drug-related death. Two thousand four hundred and fifty-four of these cases were suspected drug-related deaths at autopsy, and the final cause of death was determined to be drug-related making these our true-positive (TP) cases. Two hundred and sixty-five cases were suspected to be drug-related fatalities at autopsy but were found to have an alternative final cause of death unrelated to drugs, making these cases our false-positive (FP) cases. One hundred and fifteen cases had no suspicion for drug involvement at autopsy but after toxicological analysis were determined to have a drug toxicity as final cause of death, designating these our false-negative (FN) cases. One hundred and twenty-two cases had no suspicion of drug-related death at the time of autopsy and had an alternative cause of death unrelated to drugs, designating these our true-negative (TN) cases. The following data are displayed in Table 1. We calculated the sensitivity, specificity, false-positive rate, and false-negative rate for our study as follows: sensitivity: 95.52%; specificity: 31.52%; false-negative rate: 4.48% and false-positive rate: 9.75%.

From our findings, based on the sensitivity, the investigators were able to correctly predict a suspected drug-related fatality prior to autopsy in greater than 95% of cases. There were a few cases present, however, with a high suspicion of being a drug-related fatality that had an alternative cause of death unrelated to drug involvement resulting in a false-positive rate of 9.75%. This false-positive percentage is significant because it represents the number of cases that could have been misclassified as drug-related deaths if only investigative findings, toxicological analysis, and external examination were performed. A full autopsy of these cases yielded another more significant cause of death

TABLE 1. The Classification of Cases Based Preliminary Suspension of Drug Involvement Prior to Autopsy vs the Final Cause of Death Being Drug Related

Table of Preliminary Finding and Final Declaration

	Final Finding: Overdose Deaths?		
Preliminary findings	Yes	No	Total
Overdose: Yes	2454	265	2719
Overdose: No	115	122	237
Total	2569	387	2956

such as disease processes or injuries listed in Adelson's class I category, which are processes that are catastrophic and will cause death regardless of other pre-existing states.[17] Examples of class I processes encountered in this study included pulmonary emboli, ruptured gastric ulcer, ruptured berry aneurysm (without stimulants in the body at the time of death), and a compressive subdural hematoma with a manner of death classification of homicide.

Additional data extracted from this extensive review of cases and available toxicology results included the four most common illicit drug trends within our region over this 6-year period (Fig. 2). Heroin, fentanyl, methamphetamine, and cocaine were found to be the most common illicit drugs involved in our overdose deaths. Heroin was the most common illicit drug found in our overdose deaths in 2016 but steadly declined over the 6-year period, where as the opposite pattern is observed with fentanyl and methamphetamine. Fentanyl, and to a lesser degree methamphetamine, significantly increased over this same 6-year period becoming the leading illicuit drugs involved in overdose fatalities within our region. The involvement of cocaine in these deaths remained consistant over this time frame.

DISCUSSION

The results of this study support a correct determination in drug-related deaths based on scene investigation, external examination, and comprehensive toxicologic results in a majority of cases. A few cases, however, were found to have an alternative cause of death apart from drug involvement. These cases may have been misclassified as drug-related deaths if a standard autopsy were not preformed. The authors found a few other studies similar in scope to this study but differed in their methodology and the tools at their disposal. In one study, the authors looked at the percentage of negative toxicologic results for external examinations with comprehensive toxicologic analysis that were performed for suspected drug-related fatalities in comparison with cases of suspected drug-related deaths that underwent a standard autopsy that had an alternative cause of death not involving drugs within a single year. This same study then retrospectively reviewed all drug-related cases from a year in which a standard autopsy was done on all drug-related fatalities and determined what percentage of those cases had an alternative cause of death other than drugs. In both instances, the authors found an 11% to 13% rate where the toxicologic analysis detected no substances to explain the cause of death with the conclusion that another cause of death other than drug-related had occurred.[18] In a second similar study, 60 cases that included accidental deaths due to drug toxicity and natural deaths were selected and analyzed out of 629 cases chosen by a case management database. These cases were selected for blind review by three pathologists, and the pathologists were given the following information: patient's history information about the scene investigation, external examination findings, and results from the toxicology report to determine if these 3 pathologists could correctly classify the cause and manner of death in these cases of suspected drug toxicity. The outcome of this study revealed that although these pathologist could determine the correct cause and manner of death is 75% to 80% of the cases without internal examination findings, this was not effective as combing investigation, autopsy, and toxicologic findings when addressing deaths due to suspected drug toxicity.[19]

Whereas another study done with the purpose of decreasing the number of high risk autopsies being performed in a select population such as intravenous drug users referrals for human immunodeficiency virus/hepatitis C infection, positive decedents found that with the use of external examination, toxicology, and/or postmortem computed tomography, it is possible to reduce the number standard autopsies done in this select group by two-thirds.[20]

A standard autopsy is without a doubt the most accurate method to reveal a decedent's cause of death or to rule out alternative causes of death in drug-related deaths; however, as the number of practicing pathologists declines and workplace shortages continue to exist, the increase in drug-related deaths tempt offices to perform external examinations and draw specimens for toxicologic testing in lieu of a standard autopsy.[21–23] This study points out the risks of only using investigative findings, personal history, external examination, and comprehensive toxicology to try to accurately ascertain the correct cause of death in all suspected drug-related fatalities.

The results of this study may help medical examiner/coroner offices to acquire additional resources, including other investigative modalities like advanced imaging techniques, namely, computed tomography (CT). Studies have shown the use of postmortem CT to be extremely beneficial as a triage tool in identifying various injuries secondary to trauma such as subdural hematomas, gunshot wounds, and injuries from motor vehicle accidents. The use of postmortem CT is also very useful in the detection of some of most common natural causes of death such as ruptured myocardial infarcts, saddle pulmonary thromboemboli, hemoperitoneum

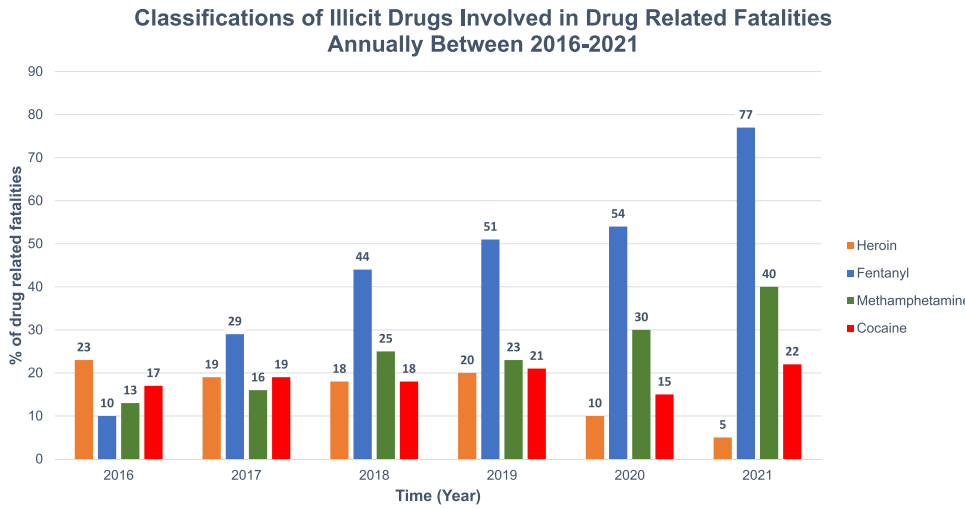

FIGURE 2. The four most common illicit drugs involved in drug-related fatalities within our region annually from 2016 to 2021.

from a perforated gastrointestinal ulcer, and a rupture aortic aneurysm etc. There are, however, certain disease states such as ischemic heart disease, less obvious pulmonary emboli, and, in some cases, strangulation by hanging that did not have obvious osseocartilaginous injuries, in which postmortem CT was not as sensitive in its ability to accurately diagnose these disease processes.[24,25] Therefore, the utility of postmortem CT in drug-related fatalities, as a triage tool with investigative findings, history, external examination, and full toxicology, could potentially pose a better alternative to a standard autopsy in specific cases. This approach could also help to preserve resources while minimizing the number of cases that could be misclassified without a full autopsy.

This study has some limitations. One limitation is that the authors made the assumption that the cause of death determined by the forensic pathologist assigned the case was correct. A second limitation was if illicit drugs were present at the time of death, they were at least thought to contribute to the death except for those deaths with class I natural or traumatic processes. Another limitation was the population sample used in this study which only reflects western North Carolina demographics, which may differ from other regions in the country.

CONCLUSIONS

As drug-related fatalities continue to rise, the strain to meet the demand for autopsies among medical examiner and coroners offices across the nation is also mounting. This study was done first and foremost for informational purposes in an attempt to determine the accuracy in our region of using investigative findings, comprehensive toxicology, and an external examination in place of a standard autopsy and what sort of cases if any could potentially be misclassified as drug-related deaths if the standard autopsy were not performed in these cases. As it currently stands, our false-positive rate was almost 10%, which is still a significant number of cases that could have resulted in misclassification. With the access and application of imaging modalities such as postmortem computed tomography, it might be possible to further reduce the risk of misclassifying these false-positive cases by making alternative standards to preforming a standard autopsy plausible in special circumstances. As circumstances currently stand, many medical examiner/coroner offices do not have access to such modalities. As a result, these data can be useful in starting discussions, making decisions regarding standard policies and procedures, as well as confirming correlations in drug trends in other offices. The purpose of these data is not to sway offices to adopt one practice over another but to serve as an additional source of information when making such important decisions.

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