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Investigation of Postmortem Methamphetamine Cases Submitted to the New York City Office of Chief Medical Examiner

A thesis presented in partial fulfillment of the requirements for the degree of

Master of Sciences in Forensic Science.

John Jay College of Criminal Justice

City University of New York

Isaiah Jewell

August 2021

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A thesis has been presented to and accepted by the Office of Graduate Studies, John Jay College of Criminal Justice in partial fulfillment of the requirements for the degree of Master of Sciences in Forensic Science.

John Jay College of Criminal Justice

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Abstract

Methamphetamine (N-methylamphetamine) is a central nervous system stimulant (CNS) and sympathomimetic drug with a high addiction potential. In the United States, there has been a significant increase in the presence of methamphetamine in recent years, specifically in the Northeastern region of the country. The New York City Office of Chief Medical Examiner (NYC-OCME) postmortem methamphetamine casework from 2018 and 2019 was analyzed and revealed that the presence of the drug increased drastically within a span of one year, jumping from 65 cases in 2018 to 99 cases in 2019. Males were overwhelmingly responsible for much of the casework, taking up 141 (85.9%) of the cases across both years. The average age of an individual in this study was 41.73 years, with a standard deviation of 12.74 years. The average methamphetamine and amphetamine concentrations in all 164 cases was 1.23 mg/L and 0.17 mg/L, respectively. The mean concentration ratio between the drugs from metabolite to parent was 0.14. Polysubstance use among methamphetamine users is quite common and was apparent in the data which showed that out of all 164 cases, 129 users had used other drugs in combination with methamphetamine (78.7%). The four most common drugs seen in combination with methamphetamine across both years were ethanol, fentanyl, cocaine, and morphine being 41 (25%), 36 (22%), 35 (21%), and 28 (17%), respectively. Postmortem methamphetamine casework from the NYC-OCME can be explored and eventually built upon in future studies to further deduce other patterns and trends correlating to methamphetamine use.

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1. Introduction

Methamphetamine (N-methylamphetamine) is a central nervous system (CNS) stimulant and sympathomimetic drug with a high addiction potential. Medicinally, methamphetamine has been integral in the treatment of attention deficit hyperactive disorder (ADHD), where it is prescribed as Desoxyn. It can also be used to treat obesity and depression due to its ability to provide effects such as increased heart rate, heightened alertness, energy, and happiness (Henning et al., 2019). Though methamphetamine may act as a viable treatment method for the previously listed disorders, it has adverse side effects that may result in agitation, psychosis and even death. Methamphetamine has had a notable increase in misuse patterns in recent years. This increase can be attributed to a multitude of factors, such as manufacture of the drug, availability and socioeconomic status. The misuse of methamphetamine is a global issue, with a heightened presence in the Midwestern and Southern regions of the United States, along with a growing presence in the Northeastern region of the country.

In the United States, there has been a significant increase in the presence of methamphetamine in recent years, with an upward trend from about 160,960 cases in 2011 to 386,272 reported cases in 2018 (U.S. Drug Enforcement Administration & Diversion Control Division, 2019b) and 417,867 in 2019 (U.S. Drug Enforcement Administration & Diversion Control Division, 2020). Figure 1 shows the trend of the number of drug reports of methamphetamine compared to THC and cocaine from 2001 to 2019. The figure indicates that methamphetamine is on a relatively steep upward trend and will likely continue to do so, while THC and cocaine have been declining.

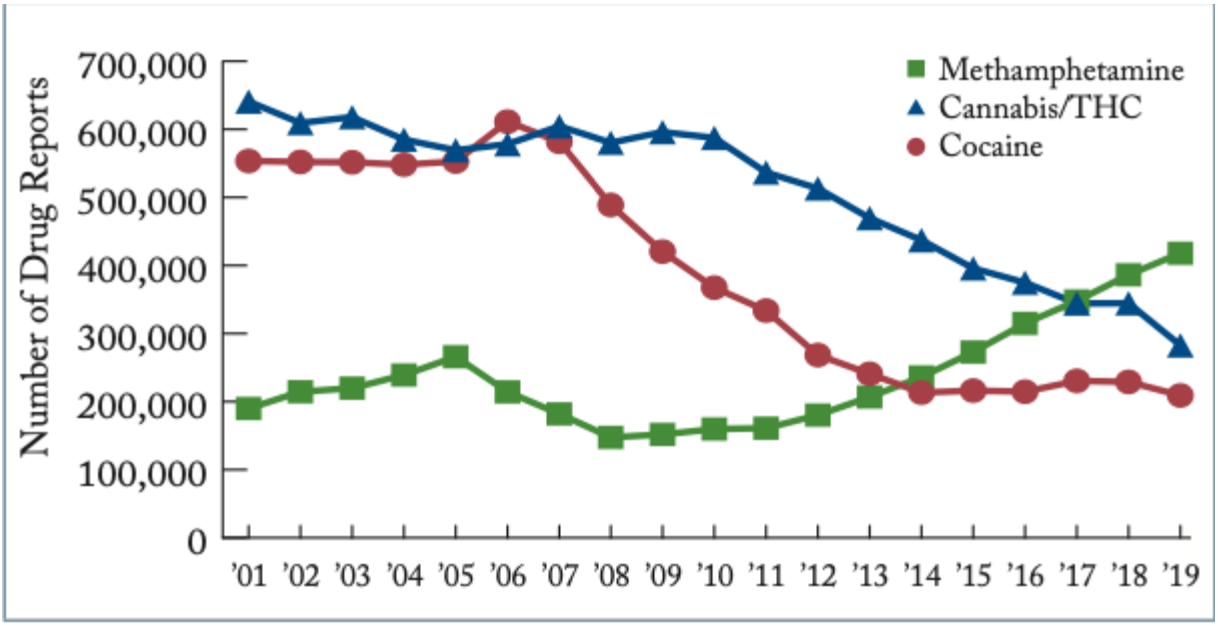


Figure 1. NFLIS-Drug 2019 annual report on national trend estimates for methamphetamine, THC, and cocaine from January 2001-December 2019. Image acquired from: https://www.nflis.deadiversion.usdoj.gov

The highest presence of methamphetamine typically has occurred in the Western, Midwestern and Southern regions of the country; however, a 2019 annual drug assessment report by the Drug Enforcement Agency (DEA) has noted an increased presence of the drug in the Northeastern region (U.S. Department of Justice & Drug Enforcement Administration, 2019). NFLIS data from New York City regarding drug seizures by law enforcement noted a drastic increase in methamphetamine reports from 529 seizures in 2015 to 729 seizures in 2016, which was a 37% increase (U.S. Drug Enforcement Administration & Diversion Control Division, 2017). The continuous upward trend in the presence of methamphetamine could be directly correlated to the price and potency of the drug. A major highlight to the published drug assessment report created by the DEA was the price of methamphetamine dropping from $68 to $56 per gram from January 2013 to December 2017, with an average purity and potency being well over 90% (U.S. Drug Enforcement Administration & Diversion Control Division, 2019a). The cheap value and high potency of the drug will push drug misusers to use methamphetamine as long as it remains easily attainable at a low rate in the drug market.

In three surveys taken by the National Survey on Drug Use and Health (NSDUH) (Substance Abuse and Mental Health Services, 2019) between 2015 and 2018, which includes a variety of

different factors including sex, age, race, education, household income, sexuality, and mental illness, among others, it was noted that roughly 6.6 in 1,000 Americans have used methamphetamine within a year between 2015 and 2018 (Jones et al., 2020a; Substance Abuse and Mental Health Services Administration, 2019). The report by Jones et al. (2020a) also noted that among the several surveys conducted by the NSDUH, roughly 59.7 in 1,000 Americans have used methamphetamine in their lifetime, which is significant when adjusted to the general American population, equating to roughly 14,686,900 Americans. The use of methamphetamine is highly correlated with polysubstance misuse, particularly those who use heroin and other opioids. Further analysis on NSDUH surveys between 2015 and 2018 noted an increase in methamphetamine use particularly in those who have used heroin and LSD within the past year, specifically a 66.2% and 100.4% increase, respectively (Palamar et al., 2020).

In an anonymous survey collected from drug treatment programs in the United States, there was a significant increase in the use of methamphetamine between 2011 and 2017 for treatment-seeking opioid users, jumping from 18.8% to 34.2% in just six years (Ellis et al., 2018). A similar type of trend was noticed from the Treatment Episode Data Set (TEDS) from 2008 to 2017, in which methamphetamine misuse in heroin users jumped from one in 50 to one in eight (Jones et al., 2020b). Recent data has also suggested that fentanyl has heavily contributed to the rise in methamphetamine use. An article published regarding public health in which urine drug test results of 1,050,000 patients collected by health care professionals as part of routine care noted a 2.20% to 30.37% increase in positive methamphetamine results between 2013 and 2019 for those who also tested positive for fentanyl (Twillman et al., 2020). Figure 2 shows the number of overdose deaths involving psychostimulants (methamphetamine) and opioids from 1999 to 2017, and Figure 3 the overdose deaths due to psychostimulants, mainly methamphetamine.

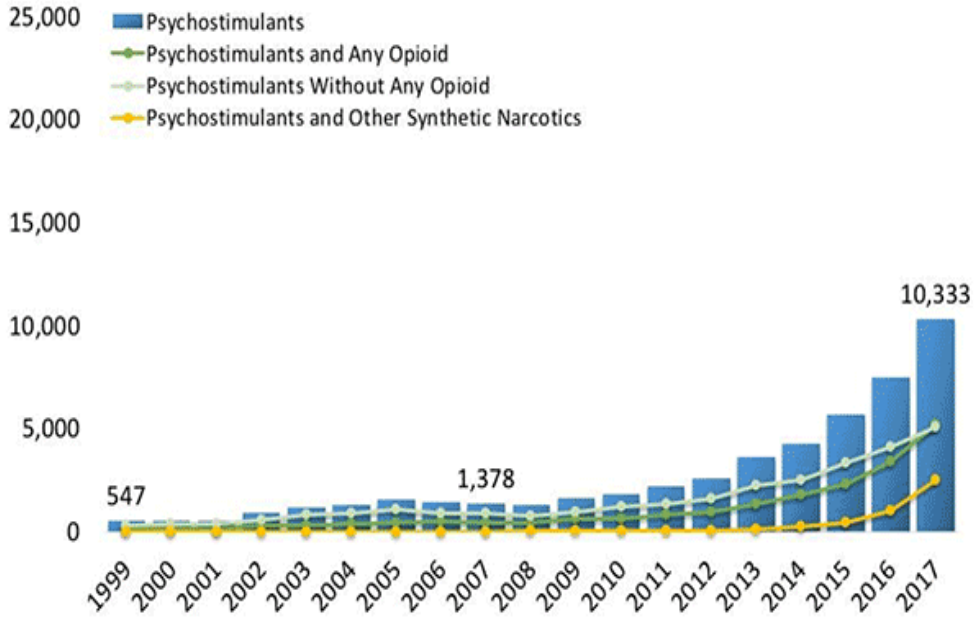


Figure 2. National drug overdose deaths involving psychostimulants with abuse potential (including methamphetamine) by opioid involvement. from 1999-2017. Image acquired from: https://www.drugabuse.gov

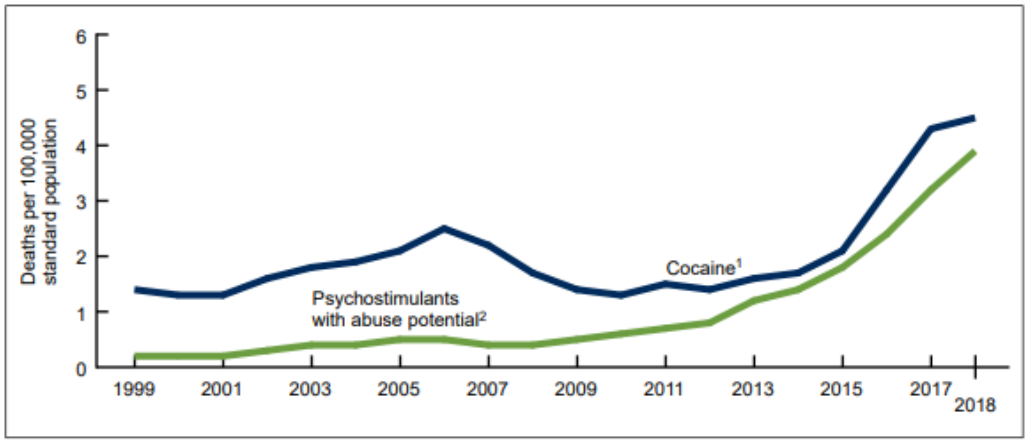


Figure 3. CDC data on drug overdose data pertaining to cocaine and psychostimulants, such as methamphetamine, amphetamine and methylphenidate. Image acquired from: https://www.cdc.gov

Chemically, methamphetamine exists as two enantiomers, specifically dextro-methamphetamine (D-methamphetamine) and levomethamphetamine (L-methamphetamine). See

Figure 4. D-methamphetamine is considered to be psychoactive and thus is the enantiomer most commonly misused, as well as the racemic mixture of the two enantiomers.

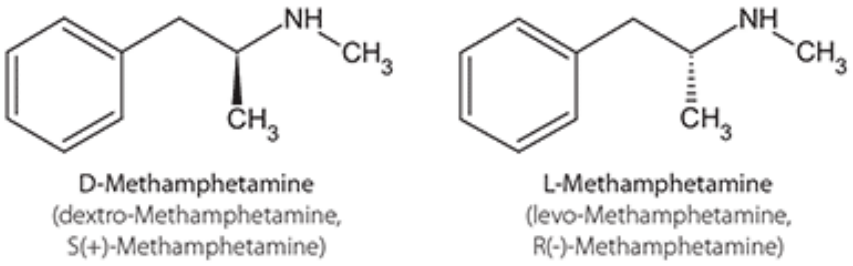


Figure 4. Depiction of D and L methamphetamine enantiomers. Image acquired from: https://www.sigmaaldrich.com/

Pharmacologically, methamphetamine's mechanism of action consists of increasing dopamine release and blocking dopamine reuptake in the brain, providing intense euphoria, as well as increasing synaptic levels of serotonin (5-HT) and norepinephrine (NIDA, 2021; United States, 2005). The increased levels of serotonin can produce delusions and psychosis, while increased levels of norepinephrine can be associated with alertness and other sympathomimetic effects (United States, 2005).

The route of administration of methamphetamine (oral ingestion, snorting, smoking, etc.) varies geographically and each method results in differing onset times; however, the drug's effects last roughly on average 8-12 hours (NIDA, 2021; Courtney & Ray, 2014). Methamphetamine is primarily metabolized in the liver into 4-hydroxymethamphetamine and amphetamine, then further metabolized into several metabolites such as 4-hydroxyamphetamine, norephedrine, 4-hydroxynorephedrine and hippuric acid (Courtney & Ray, 2014). See Figure 5. It is excreted by the kidneys with roughly half of the dose (30-50%) remaining as unchanged methamphetamine, 10% being amphetamine and 15% being 4-hydroxymethamphetamine (Courtney & Ray, 2014).

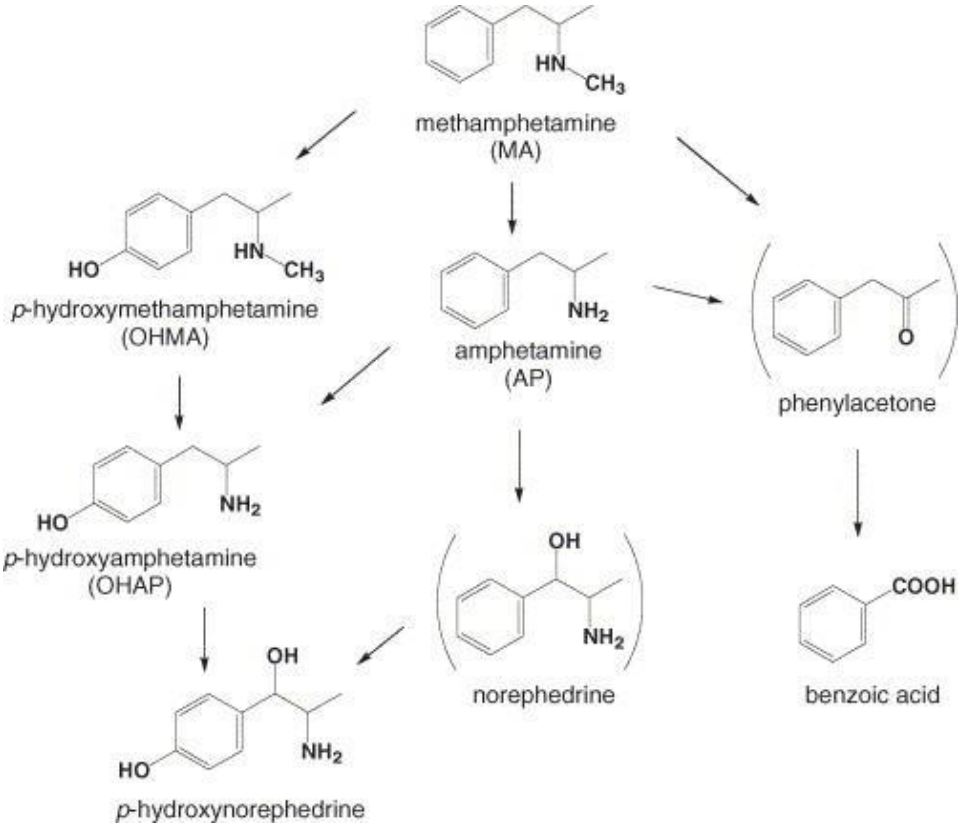


Figure 5. Methamphetamine metabolic pathway. Image acquired from: Kanamori, T. et al., 2005.

Low-moderate therapeutic doses of methamphetamine typically range from 5-40 mg, while illicit use is upwards to 50 mg and higher (Cruickshank & Dyer, 2009). Therapeutic doses of methamphetamine ranging from 20 to 40 mg per day in divided doses lead to peak blood concentrations less than 0.2 mg/L (Logan, 2001; Prakobsrikul et al, 2019). Previously reported lethal blood concentrations of methamphetamine may be slightly higher, with concentrations ranging from 0.6-5.0 mg/L; however, these concentrations may depend on other factors, such as an individual's tolerance (Kiely et al., 2009), and an overlap between therapeutic and lethal concentrations can be observed. In many pathological examinations of individuals found with methamphetamine in their system, the cause of death was due to underlying cardiovascular diseases, such as coronary artery atherosclerosis or even sudden cardiac arrest from acute myocardial infarction (Lewis et al., 2021a; Paknahad et al., 2021).

Interpretation of postmortem concentrations of methamphetamine are particularly challenging due to the fact that methamphetamine undergoes postmortem redistribution (PMR). PMR refers to

changes in drug concentration throughout an individual's body after death due to passive diffusion of drugs between tissue and blood, typically from areas of high to low concentrations (Drummer, 2004). Heart blood concentrations are generally more affected by PMR than femoral blood concentrations. Due to this, the estimation of antemortem methamphetamine concentrations from postmortem blood is not recommended because there is a high error rate associated with the correlation (Lewis et al., 2021b). Methamphetamine is a basic drug (pKa 9.87), and although it is not highly lipophilic (Log P 2.07) and it shows a low protein binding (Fb 0.1-0.2), it has a high volume of distribution (3-7 L/kg), which may explain the PMR of this drug (Baselt, 2017). Because of this, postmortem concentrations of the drug must be carefully considered.

In a published article highlighting three case reports on peripheral blood, it was suggested that the postmortem femoral blood concentration of methamphetamine and amphetamine are roughly 1.5 times higher than antemortem concentrations (McIntyre et al., 2013). In another published article, it was shown that when comparing postmortem blood concentrations to that of antemortem, the femoral vein, subclavian vein and cardiac blood each had a ratio of 1.4, 1.63 and 1.96, respectively (Lewis et al., 2021b). However, although it is not recommended based on varying degrees of PMR, McIntyre et al. suggested that comparisons of postmortem and antemortem concentrations may be done when blood is collected from at least two areas of the body, specifically a peripheral area and a central area, such as the heart, and if the ratio of the two sites is approximately 1.6 (McIntyre et al., 2013). In the United States, postmortem methamphetamine research is limited (Logan, 1998), however previous research performed in Australia (Kaye et al., 2008), Iran (Paknahad et al., 2021), Thailand (Prakobsrikul et al, 2019) and Saudi Arabia (Al-Asmari, 2021) reported postmortem methamphetamine concentrations as well as demographic information on those cases.

The goal of this study was to investigate methamphetamine deaths in New York City (NYC) between 2018 and 2019 utilizing casework from the Office of Chief Medical Examiner (OCME). Various aspects of information were explored, such as demographics, cause and manner of death, and the presence of other drugs in combination with methamphetamine. Further statistical information was derived through computed analysis software to explore and compare methamphetamine concentrations in different groups. Ultimately, exploring the postmortem methamphetamine data from the NYC-OCME will provide useful information to improve the toxicological interpretation of postmortem cases involving this psychoactive drug.

2. Materials and Methods

2.1. Cases

NYC-OCME provided a summary of postmortem methamphetamine cases from 2018 and 2019. Data was provided within a Microsoft Excel file and included the medical examiner case number, the forensic toxicology case number, NYC borough, sex, age, ethnicity, manner of death, cause of death, if there was multi-drug usage in a case and the concentrations for several drugs in mg/L or ng/mL in femoral blood.

For the 2018 data, the drugs included in each case file were amphetamine, methamphetamine, 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), 4-aminophenyl-1-phenethylpiperidine (4-ANPP), 6-methoxy-2-naphthylacetic acid (6-MNA), 6-monoacetylmorphine (6-MAM), 7-aminoclonazepam, acetylfentanyl, acetone, alprazolam, alpha-hydroxyalprazolam, β-hydroxyfentanyl, benzoylecgonine (BE), bupropion, chlordiazepoxide, chloroethane, citalopram, codeine, cocaine, dapoxetine, desalkylflurazepam, dextromethorphan (DXM), diazepam, dihydropyridine (DPH), doxepin, ephedrine, ethanol, ethylbenzoylecgonine (EBE), fentanyl, fluoroisobutyryl fentanyl, furanyl fentanyl, gabapentin, gamma-hydroxybutrate (GHB), isopropanol, ketamine, methadone, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA), morphine, n-ethylpentylone, nevirapine, nordiazepam, norfentanyl, oxazepam, oxycodone, oxymorphone, para-fluoroisobutyryl fentanyl (FIBF), phencyclidine (PCP), phenylpropanolamine (PPA), sertraline, temazepam, trazodone, and trimethoprim.

For the 2019 data, the same drugs from the 2018 data were included in each case file along with the addition of 4-chloro-alpha-PVP, 5-fluoro-MDMB-PICA, amitriptyline, etizolam, midazolam, naloxone, nortriptyline, pseudoephedrine, tramadol, and zolpidem.

2.2. Methamphetamine Analysis in Postmortem Blood

NYC-OCME qualitative and quantitative data on sympathomimetic amines was acquired utilizing solid phase extraction (SPE) followed by Gas Chromatography-Mass Spectrometry (GC-MS) on a Agilent MSD (6890 GC with 5973 Mass Spectrometer). The drugs included in the sympathomimetic amines category include amphetamine, methamphetamine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA), ephedrine (EPHD), pseudoephedrine (PSEPHD), phentermine (PHENT), fenfluramine (FEN), methylenedioxyethylamphetamine (MDEA), phenylpropanolamine (PPA) and para

methoxyamphetamine (PMA). All data was provided in blood concentrations, in which 1.0 mL of undiluted specimen was used for the analyses.

The extraction procedure was as follows:

1. 1mL of validated negative matrix was added into the tubes labeled calibrators or controls. Then 1mL of sample was added into each appropriately labeled tube.
2. After controls and calibrators were properly adjusted, 50 µL of working internal standard pool was added to all test tubes. (5 mg/L for amphetamines, except ephedrine at 10 mg/L). Internal standard concentration in each sample was 0.25 mg/L except for Ephedrine-D3, which was 0.5 mg/L.
3. 2 mL of 100 mM phosphate buffer (pH 6.0) was added, then tubes were vortexed for 15 seconds to mix.
4. Samples then underwent sonication for 20 min using an ultrasonic bath.
5. Samples were then centrifuged for 10 min at roughly 3000 rpm.
6. The supernatant was then poured into the SPE Polycrom Clin II column with nitrogen flowing at a pressure of 2-4 psi.
7. Wash steps were performed under 2-4 psi, beginning with 2 mL of de-ionized (DI) water onto the column, followed by 1 mL of methanol onto the column, then 1 mL of ethyl acetate onto the column and finally dried for 2 min at 25 psi.
8. The elution solvent was prepared by mixing CH_2Cl_2/IPA/NH_4OH (78/20/2) with IPA/NH_4OH, followed by CH_2Cl_2.
9. 50 µL of 1% methanolic HCl was added to each eluate and evaporated to dryness at 40°C.
10. 200 µL of toluene, followed by 100 µL of trifluoroacetic anhydride (TFAA) was added to each tube, which were then immediately capped and vortexed then incubated for 15 min. at 70°C in an incubation oven.
11. Tubes were then removed from the oven and allowed to cool to room temperature.
12. 2.0 mL of pH 9.8 buffer was added to each tube and vortexed for 5-10 s then centrifuged for 10 min at roughly 3000 rpm.
13. The upper toluene layer was then transferred to a glass insert in an appropriately labeled vial (indicated aliquot, toxicology number, specimen type, dilution, analyst and date). The vial was then sealed with a screw cap and is ready for MS injection.

The MS worked in selected ion monitoring (SIM) mode, and the ions used for each drug are shown in the Table 1 below. All compounds were identified based on retention time and 2 (for internal standards) or 3 (for analytes of interest) ions.

Table 1. Sympathomimetic amine compounds and their corresponding ions (*m/z*) for GC-MS SIM method. Ions in bold represent the quantifier ion.

Compound	**SIM ions (*m/z*)**
Amphetamine-D_{11} TFA	**144**, 128
Methamphetamine-D_9 TFA	**161**, 123
MDA-D_5 TFA	**280**, 136
MDMA-D_5 TFA	**158**, 163
Ephedrine-D_3 TFA	**157**, 113
MDEA-D_5 TFA	**173**, 141
Amphetamine TFA	**140**, 118, 91
Methamphetamine TFA	**154**, 110, 118
MDA TFA	**135**, 162, 77
MDMA TFA	**154**, 162, 135
Ephedrine TFA	**154**, 110, 244
Pseudoephedrine TFA	**154**, 110, 69
Phentermine TFA	**154**, 91, 132
Phenylpropanolamine TFA	**140**, 69, 230
Dexfenfluramine TFA	**168**, 140, 159
MDEA TFA	**168**, 162, 140
PMA TFA	**121**, 148, 261

2.3. Data Analysis

Utilizing the data provided by the NYC-OCME, data analysis was performed using Microsoft Excel version 16.48 and GraphPad Prism 8 Version 8.4.3. Microsoft Excel was employed to perform descriptive statistics, such as mean, median, SD, range, and to create various types of graphs. GraphPad Prism was used to determine the statistical significance of drug combinations as it relates to cause or manner of death, specifically when performing the non-parametric Mann-Whitney test and observing $p<0.05$.

Analysis of the data was broken down into several different categories. This includes the manner of death as percentages for both years, which borough most individuals in the casework were from, the sex and age range of individuals, ethnicity, whether the individuals had combined drug usage and the prevalence of a variety of drug classes.

Further analysis was performed utilizing the concentration of methamphetamine in comparison to demographics, as well as cause and manners of death. In this portion of the analysis, methamphetamine concentrations were tabulated into three different categories of death: multidrug use, methamphetamine only use, and non-drug related. This analysis was further built upon by observing methamphetamine deaths relating to homicides with the combination of cocaine.

3. Results

3.1. Demographics (sex, age, race, location)

The total number of postmortem cases received by the forensic toxicology division of the OCME was 5,704 in 2018 and 5,712 in 2019. The total number of postmortem methamphetamine cases included in this study was 164, with 65 cases from 2018 (1.1% of 2018 total cases) and 99 cases from 2019 (1.7% of 2019 total cases). The overwhelming majority of the methamphetamine cases involved males, accounting for 141 (85.9%) of the total cases between 2018 and 2019, and a total of 20 females (12.2%). The overall case breakdown between both years is depicted in Table 2.

Table 2. Age data for NYC-OCME postmortem methamphetamine cases in 2018 and 2019.

Sex	**2018 Cases (n=65)**	**2019 Cases (n=99)**
Male	53	88
Female	12	8
No available data	0	3

The ages of individuals in all of the cases ranged from 18-75 years, with an average age of 41.73 and a standard deviation of 12.74. The average male age was 42.26 years, with a standard deviation of 12.79, and the average female age was 38.8 years, with a standard deviation of 12.03. A breakdown of the ages separated by year is depicted in Figure 6.

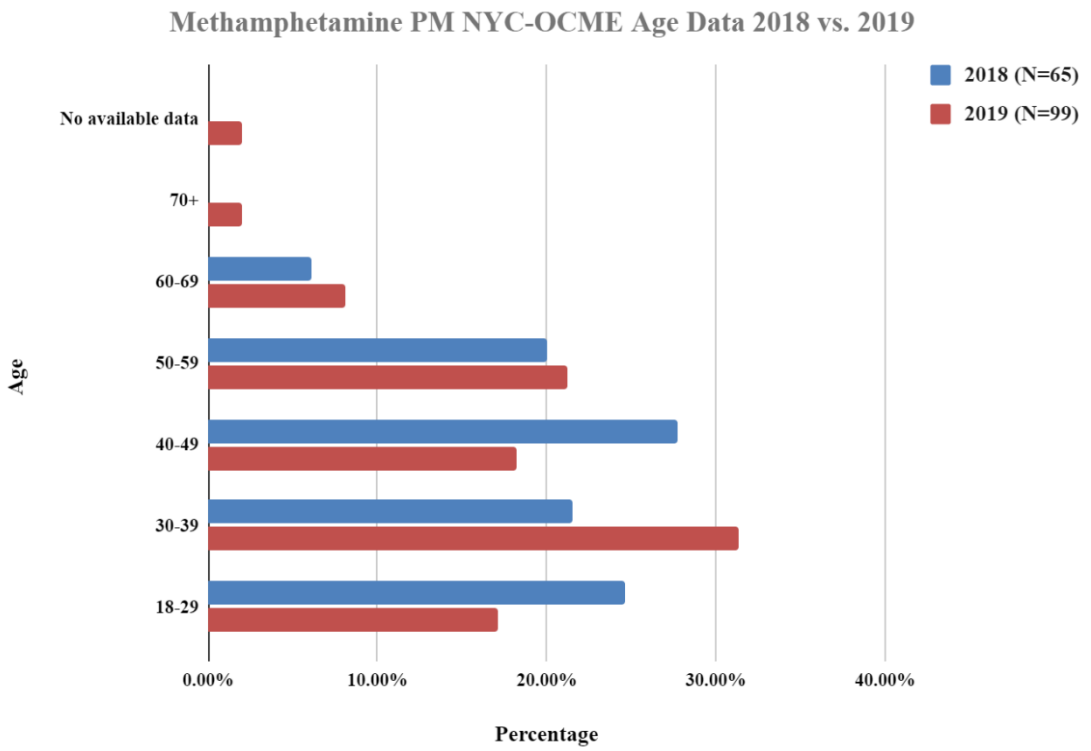


Figure 6. Age ranges of postmortem methamphetamine cases in NYC-OCME casework from 2018 and 2019.

The overwhelming majority of cases were dominated by white individuals, taking up 39% (N=64) of all cases, however a significant portion of cases were taken up by the black and Hispanic population as well, being 25.6% (N=42) and 23.2% (N=38), respectively. The ethnicity data separated by 2018 and 2019 is shown in Figure 7 below.

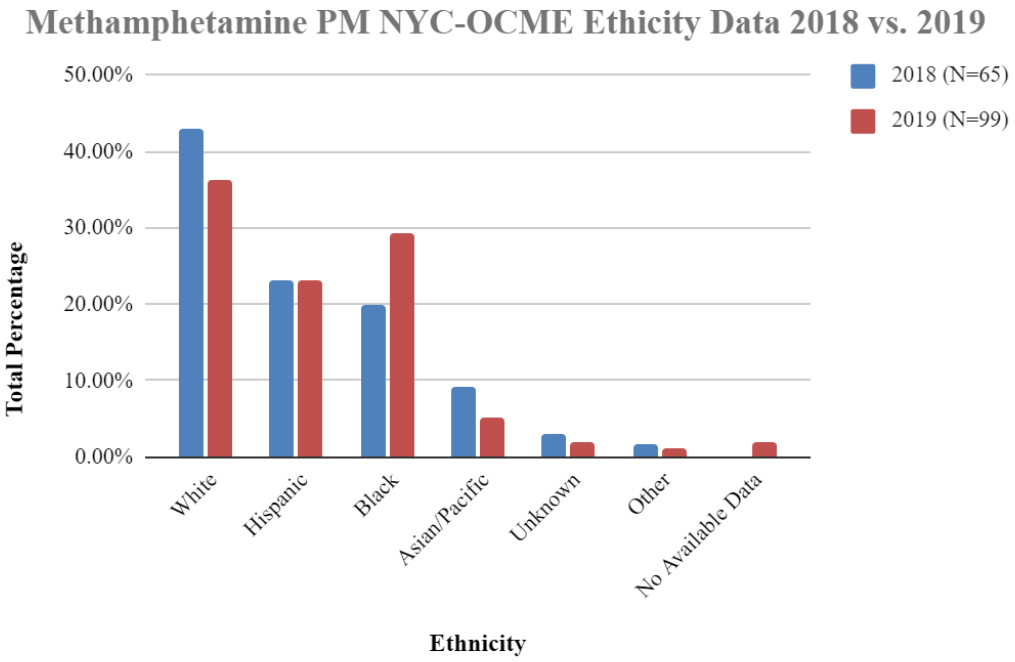


Figure 7. Ethnicity data of postmortem methamphetamine cases in NYC-OCME casework in 2018 and 2019.

The cases were also broken down by boroughs, with Manhattan showing the higher number of cases at 64 (39.0%). The borough breakdown is shown in Figure 8.

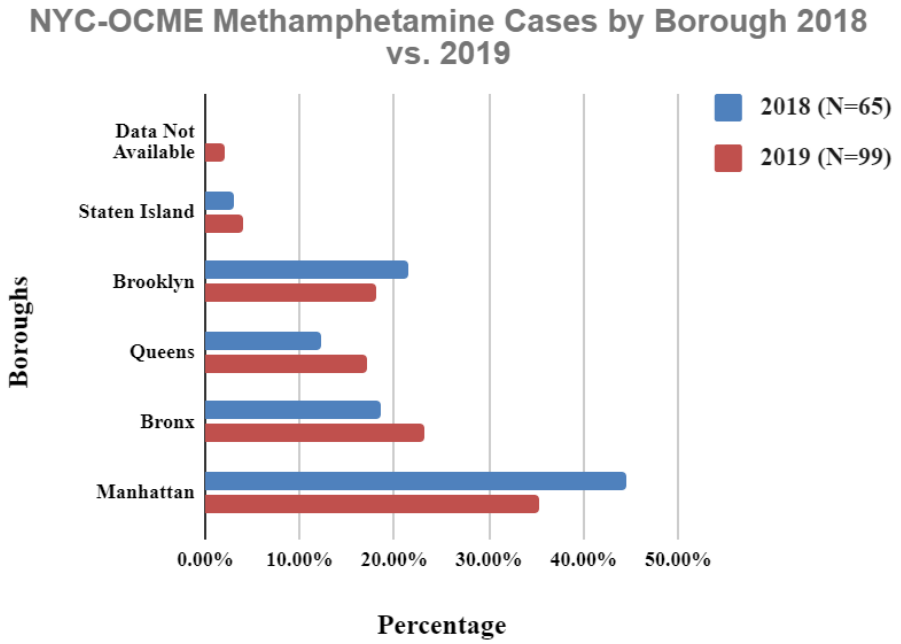


Figure 8. Borough breakdown of NYC-OCME postmortem methamphetamine casework in 2018 and 2019.

3.2. Cause and Manner of Death

Many of the cases in both years had a cause of death being acute intoxication of methamphetamine combined with other drugs (68 out of 164 total cases), or simply just acute intoxication from methamphetamine (26 out of 164 total cases). This led to accidental deaths being the leading manner of death in both years, taking up 107 of all cases (65.2%). Other examples of accidental deaths that occurred in the casework (n=18) were from underlying cardiovascular diseases and blunt impact injuries. Examples of homicidal deaths (n=24) included gunshot wounds, stab wounds, blunt impact injuries, and strangulation. Suicide deaths (n=15) were from hangings, acute drug intoxication, blunt impact injuries and incised wounds. The manner of death for both years is displayed in the two pie charts below in Figure 9. In this casework, we observed an increase in homicide cases in 2019 (21 out of 99 cases, 21%) compared to 2018 (4 out of 65 cases, 6%). This observation is in agreement with the official NYC homicide data, which reported an increase from 289 homicides to 318 from 2018 to 2019 (NYPD, 2021). On the other hand, we observed a decrease in suicide cases, 8 out of 65 (12%) in 2018 and 7 out of 99 (7%) in 2019.

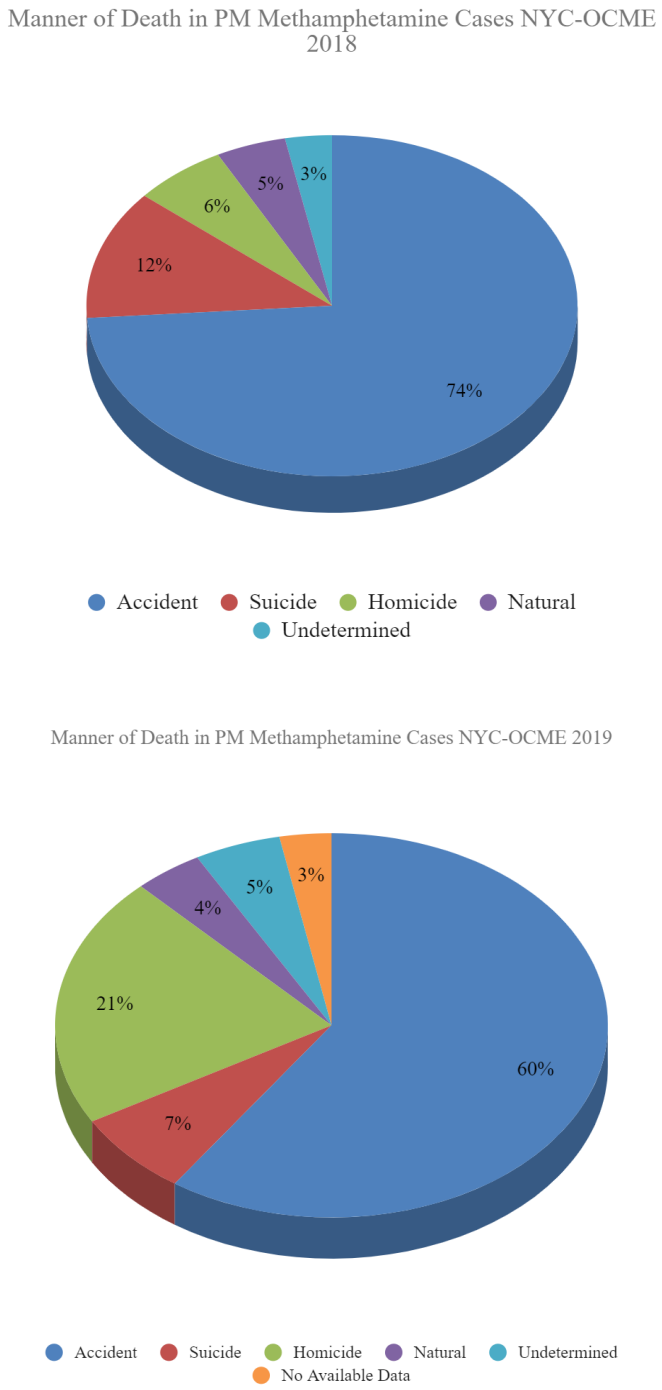
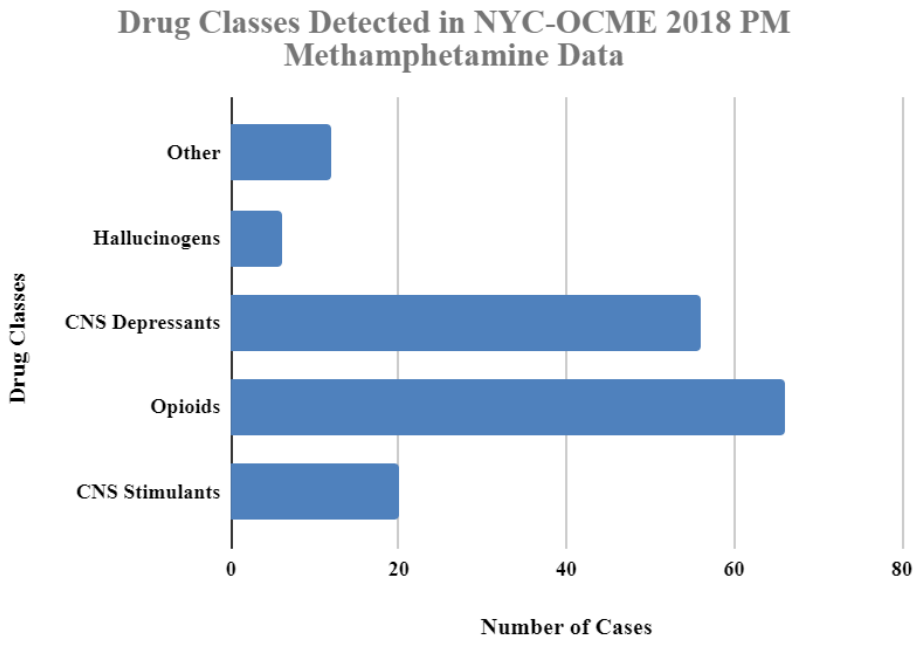


Figure 9. Manner of death for NYC-OCME casework in methamphetamine deaths 2018 and 2019.

The drugs detected in combination with methamphetamine in these postmortem cases fall under the class of CNS stimulants, CNS depressants, and opioids as well as some instances of

hallucinogens. Drugs that fall into the CNS stimulant category included cocaine and MDMA. The CNS depressant category included ethanol, GHB, and benzodiazepines, specifically alprazolam, etizolam, 7-aminoclonazepam, diazepam, oxazepam, temazepam, and midazolam. The opioids category included different compounds, such as fentanyl, fentanyl derivatives, morphine, heroin, oxycodone, oxymorphone, tramadol, and methadone. Hallucinogens included ketamine and PCP. The other category included a variety of drug classes, such as selective serotonin reuptake inhibitors (SSRIs), anabolic steroids, tricyclic antidepressants, antitussives, and prescribed drugs such as gabapentin and bupropion. Drugs detected in the casework are summarized in Figure 10. As seen in the figures below, opioids and CNS depressants were the most commonly used drug classes in combination with methamphetamine, being 118 cases (72.0%) and 109 cases (66.5%), respectively, in both years.



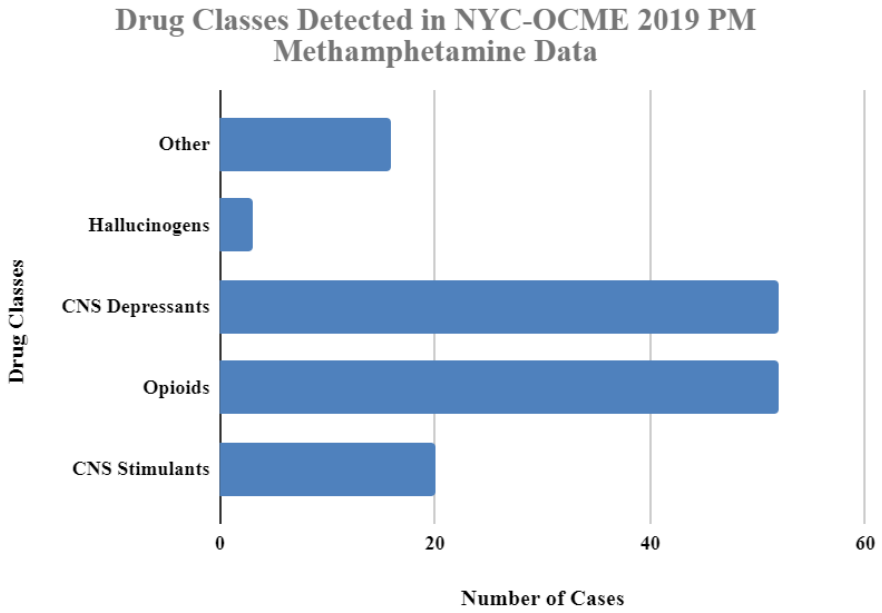


Figure 10. Drug classes detected along with methamphetamine in NYC-OCME casework in 2018 and 2019.

In 2018, 95% (62/65) and in 2019, 67% (67/99) cases had combined drug usage. In order to look more in detail into the data, the specific drugs that were most commonly used in combination with methamphetamine were narrowed down, which can be seen in Figure 11. Across both years, the leading drugs used in combination with methamphetamine were ethanol, fentanyl, cocaine, and morphine, being 41 (25%), 36 (22%), 35 (21%), and 28 (17%), respectively.

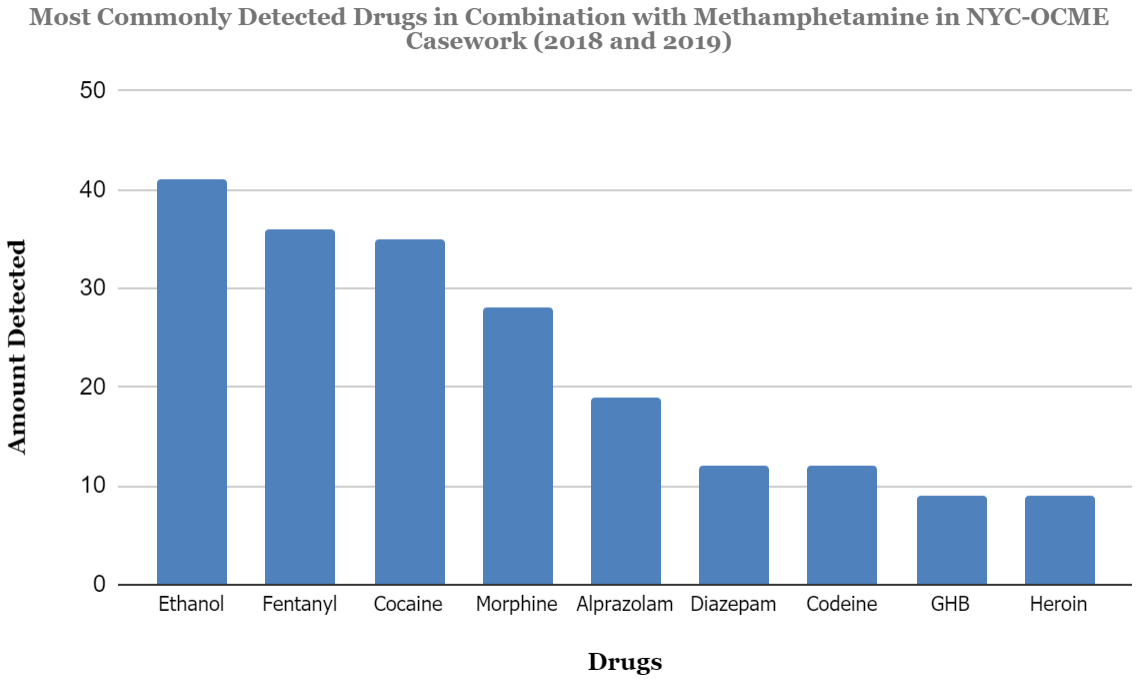
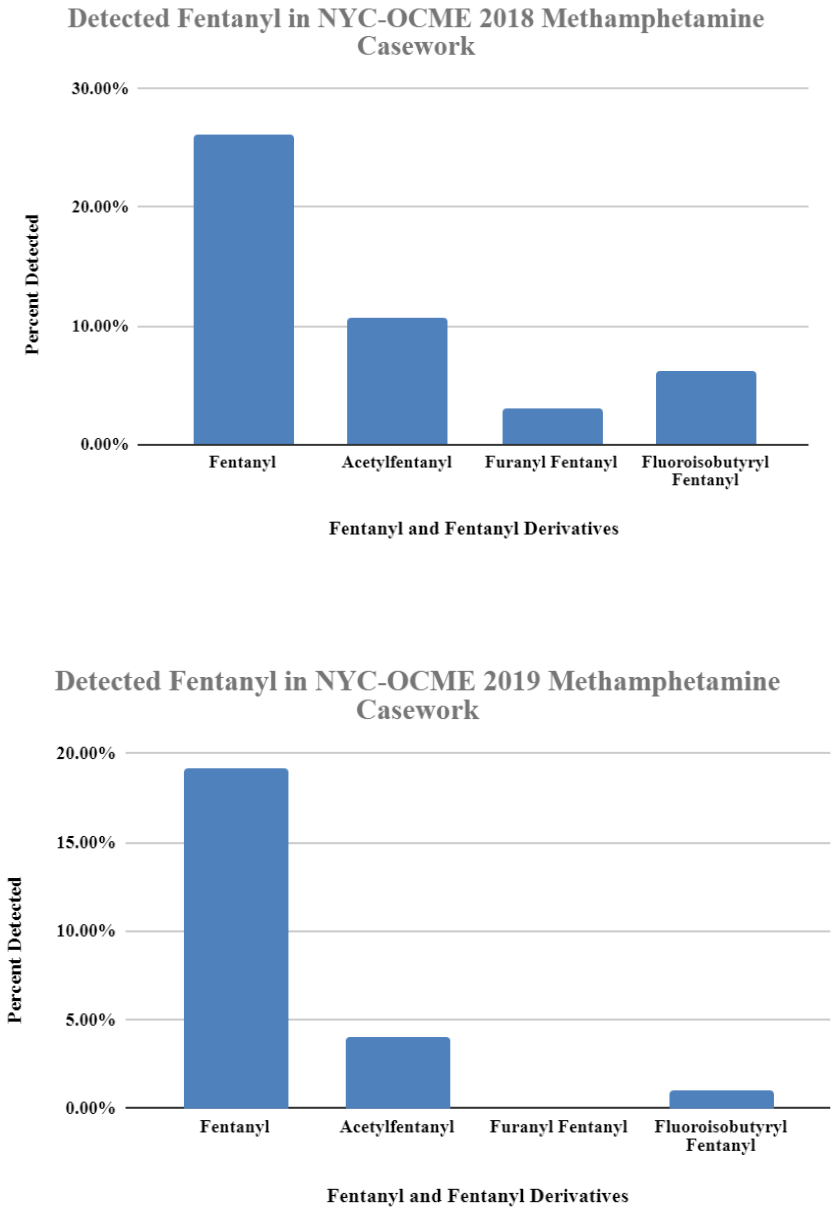


Figure 11. Most commonly seen drugs in combination with methamphetamine in NYC-OCME postmortem casework across 2018 and 2019.

Opioids were the most commonly detected drug class with methamphetamine (118 out of 164 total cases), and fentanyl in particular was the most commonly detected type of opioid in combination with methamphetamine. Figure 12 shows the number of cases that involved fentanyl and several of its derivatives, specifically acetylfentanyl, furanyl fentanyl and fluoro isobutyryl fentanyl. In both years, fentanyl was detected significantly more than any of its derivatives ($\geq$19%), and acetylfentanyl was the second most commonly detected derivative in both years. However, the percentage of acetylfentanyl cases in 2019 (4%) was lower than in 2018 (11%).



F**igure 12**. Fentanyl detected in NYC-OCME postmortem methamphetamine casework separated by 2018 and 2019.

3.3. Postmortem Methamphetamine Concentrations

The average methamphetamine and amphetamine concentrations in all 164 cases was 1.23 mg/L and 0.17 mg/L, respectively. The range of methamphetamine concentrations was from 0.1 mg/L to 25.9 mg/L, with a median concentration of 0.21 mg/L, and a standard deviation of 2.84. The range of amphetamine concentrations was from 0.1 mg/L to 1.0 mg/L, with a median concentration of 0.1

mg/L, and a standard deviation of 0.16. Utilizing the ratio of metabolite to parent drug, it was determined that the mean concentration ratio of amphetamine:methamphetamine was 0.14 (range 0.01-5.0).

In order to observe the statistical significance of methamphetamine concentration by causes of death, cases were divided in three different categories. The first category was multidrug use deaths, the second category involved only methamphetamine deaths and the third was non-drug related deaths. Data analysis was formed into a box plot and the statistical significance was determined using the Mann-Whitney test (Figure 13). Data was determined to be statistically significant if $p<0.05$. When comparing methamphetamine concentration by causes of death that were solely because of acute methamphetamine intoxication, it was significantly higher when compared to non-drug related deaths and multidrug related deaths. The statistical significance for these two comparisons were $p<0.0001$, respectively. When comparing methamphetamine concentrations between multidrug related deaths and non-drug related deaths, no statistical significance was observed ($p=0.8940$).

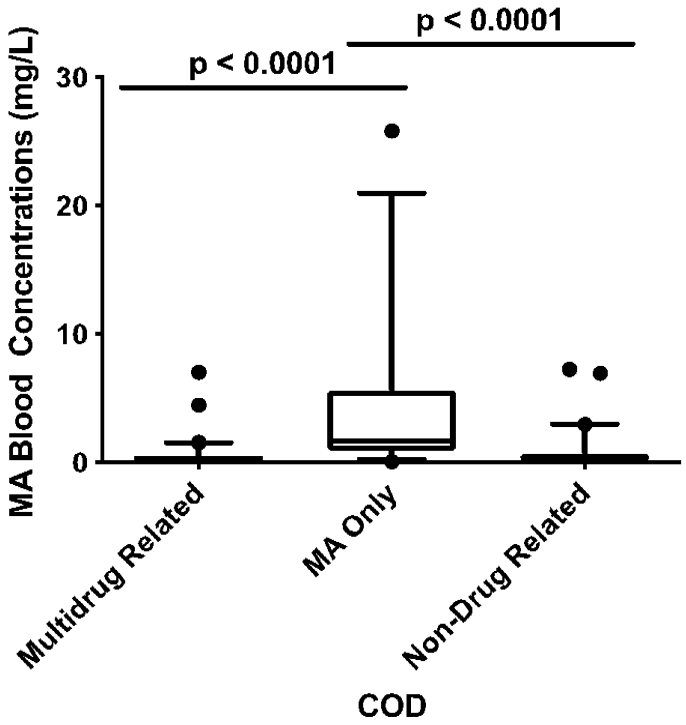


Figure 13. Box plot comparing methamphetamine concentrations by cause of death (COD).

To investigate the statistical significance of postmortem methamphetamine concentrations throughout a range of age groups, the age groups from Figure 6 were analyzed. Four individuals were excluded in this analysis due to the fact that methamphetamine was only detected in the brain of one individual (75 yrs) and no data relating to sex was available for another individual (26 yrs), and no concentration values or basic demographic information was available for two individuals. The methamphetamine concentrations of each group were compared to one another in order to see if there was a higher methamphetamine concentration value amongst any particular age group. According to Figure 14, the higher concentrations were observed in the 40-49 group; however, concentration values were only statistically significant between groups 40-49 and 60-69 ($p=0.0363$). For all the other groups, p was greater than 0.05 and determined to not be statistically significant.

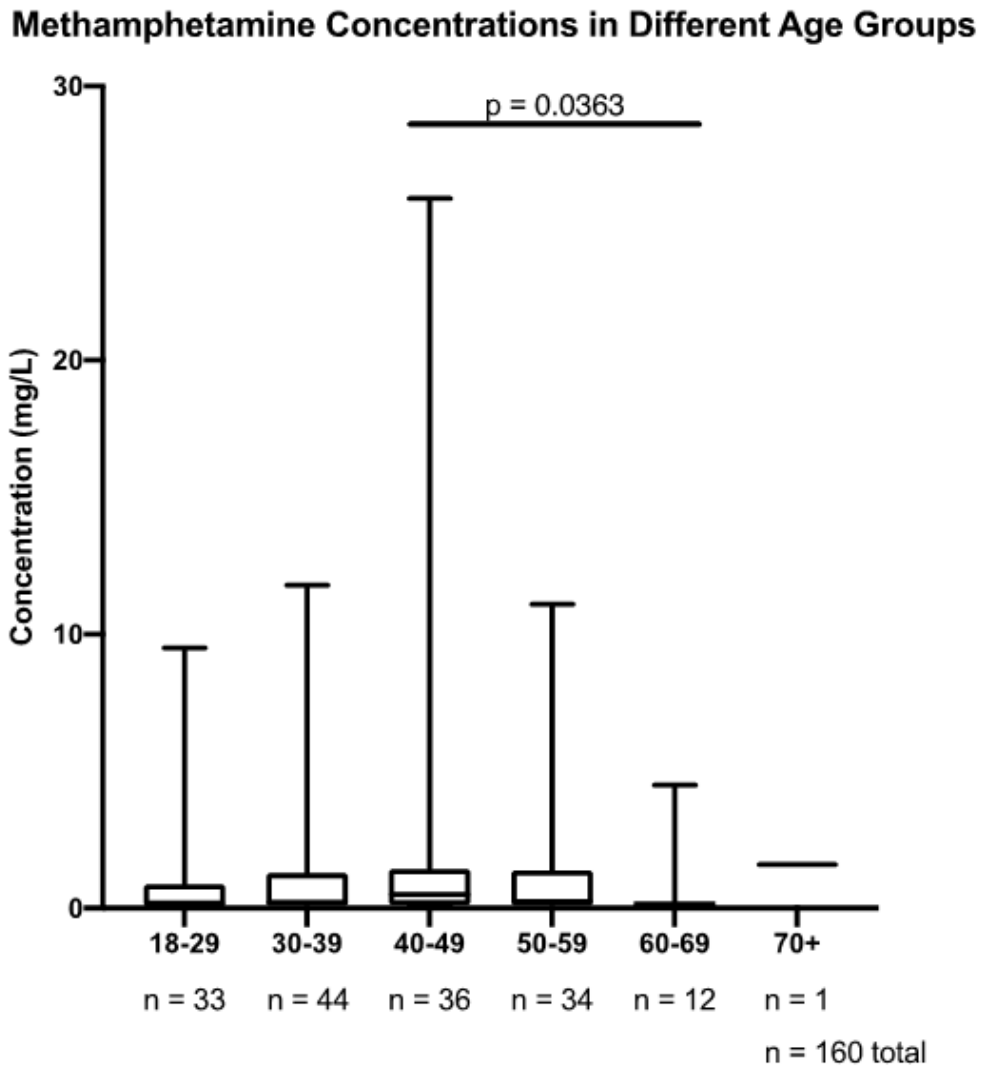


Figure 14. Box plot comparison of methamphetamine postmortem blood concentrations in various age groups.

Similar to Figure 14, postmortem methamphetamine concentrations were compared by race. Though white individuals were responsible for most of the casework analyzed, they did not appear to show higher concentrations than the other groups according to Figure 15. This statistical study was also performed across different sexes, in which no statistical significance was observed between male and female (p=0.3930). This is shown in Figure 16.

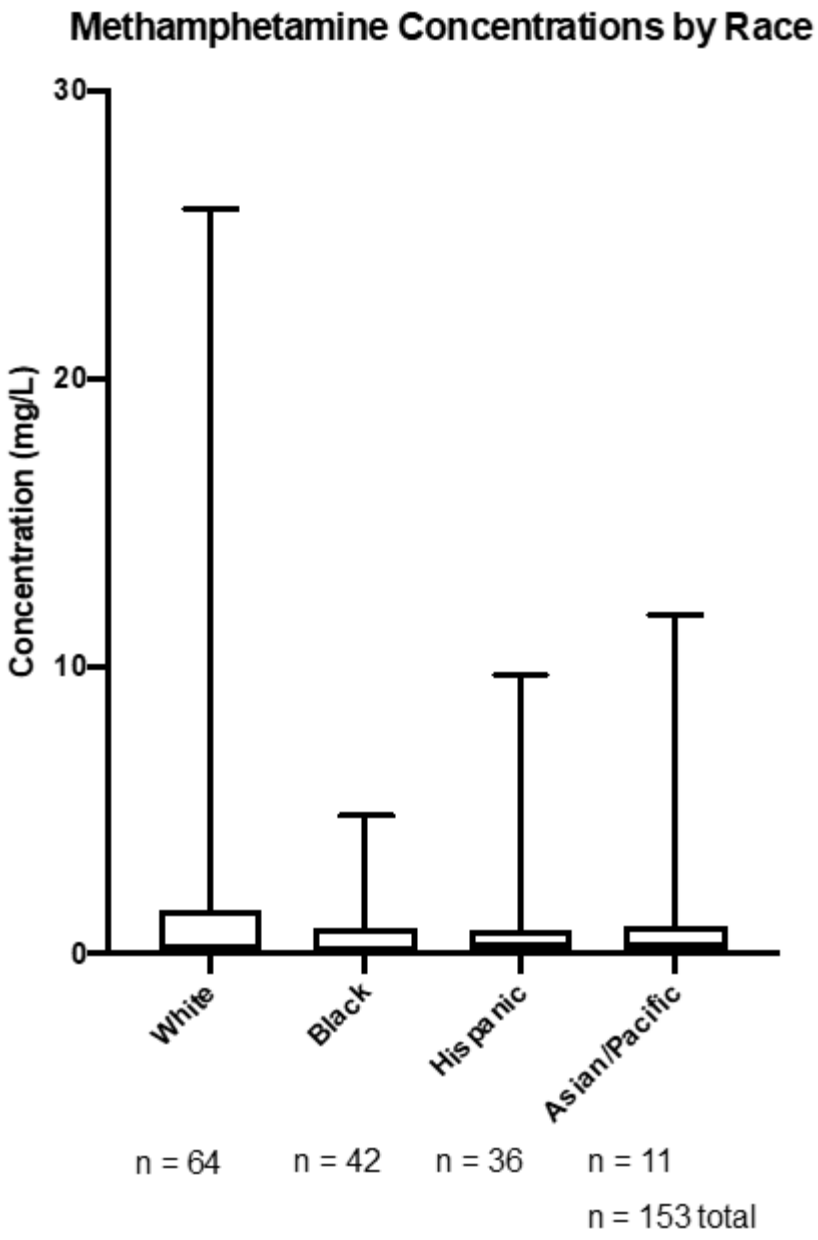


Figure 15. Box plot comparison of methamphetamine postmortem blood concentrations throughout different races.

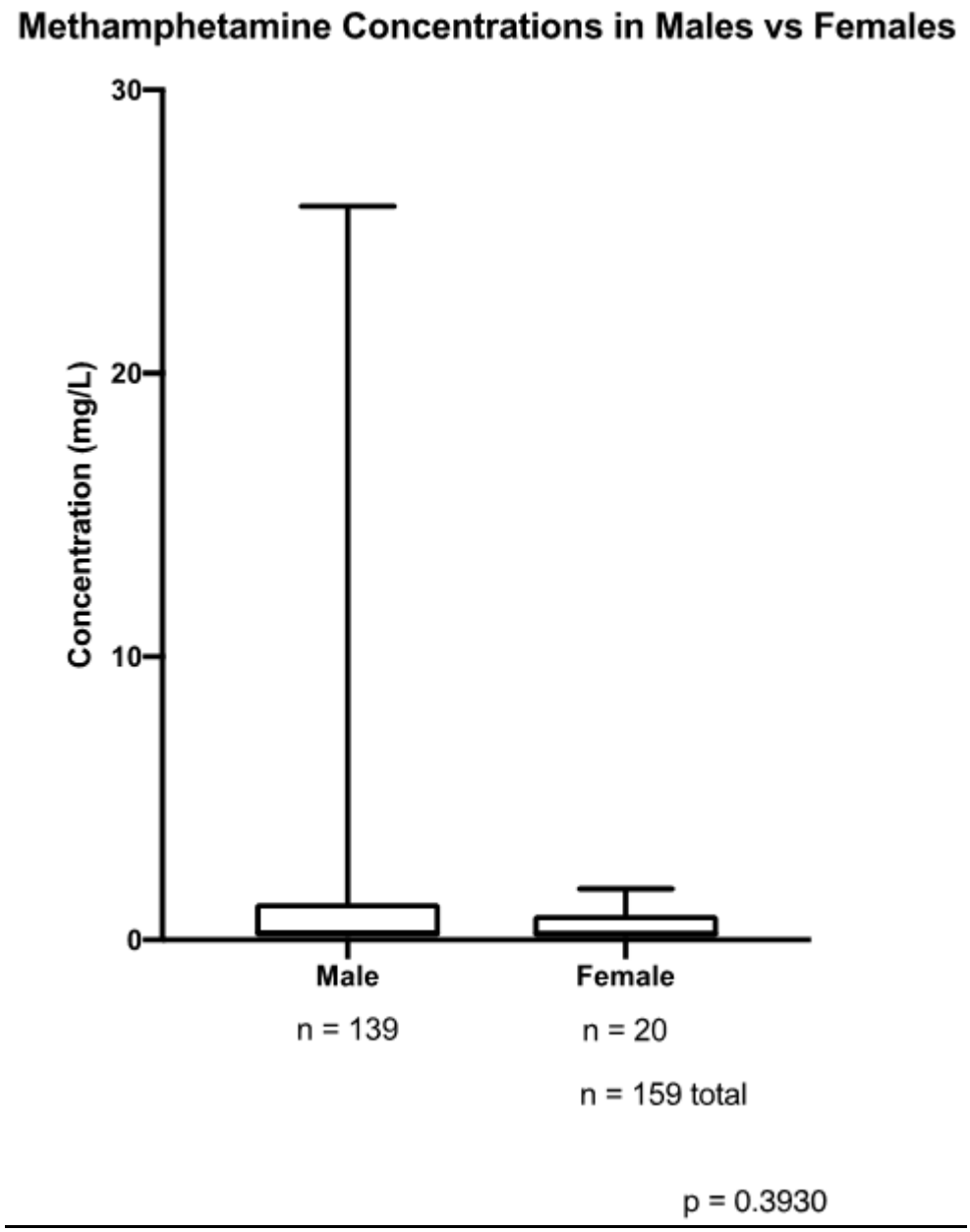


Figure 16. Box plot comparison of methamphetamine postmortem blood concentrations in males versus females.

In order to investigate the concentrations and drugs present in violent deaths (homicides), cases involving methamphetamine in combination with cocaine were plotted in box plot format. There were 35 total cases involving cocaine and methamphetamine, and only 6 of the total cases were listed as homicides. Statistical significance was tested using the Mann-Whitney test (Figure 17). When observing methamphetamine and cocaine concentrations in all types of cases involving cocaine, there was a large statistically significant difference between methamphetamine concentrations and cocaine concentrations, being that methamphetamine concentrations were higher. However, when observing the concentrations in homicide cases, there was no statistically significant difference between methamphetamine and cocaine concentrations, showing similar concentrations.

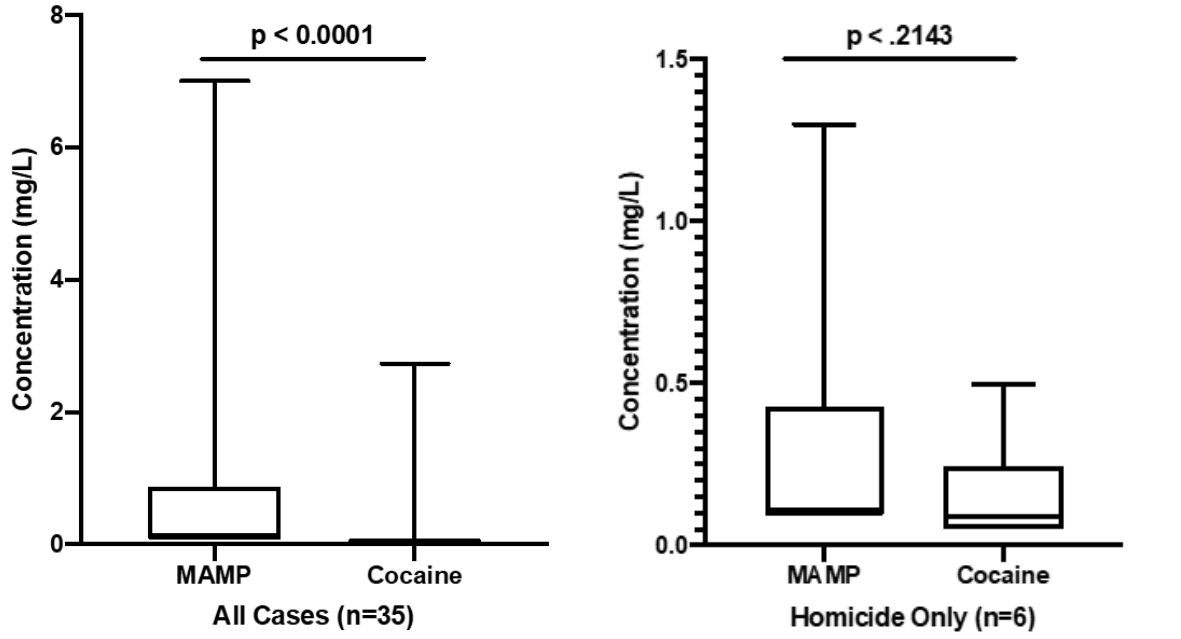


Figure 17. Methamphetamine and cocaine concentration comparison all in cases involving cocaine versus specifically cocaine in homicide cases.

4. Discussion

The results of the data analysis involving 164 total postmortem methamphetamine cases from the NYC-OCME provided important basic demographic information, as well as the potential to explore drug combinations along with concentration values determined. To reiterate highlights of the results, the average age of the methamphetamine users was 41.7 years, with males taking up 141 of the 164 total cases provided. In both 2018 and 2019, white individuals were responsible for most of the population associated with methamphetamine positive deaths and most cases were from Manhattan. Accidental deaths were the most common manner of death determined in both years, with multi-drug usage exceeding 65% in both years. Opioids and CNS depressants were the most commonly observed drugs in combination with methamphetamine; however, CNS stimulants were a large contributing factor as well. The most commonly observed drugs were ethanol, fentanyl, cocaine, and morphine, followed by various benzodiazepines. Fentanyl in particular was observed in 36 of the total cases provided in the study, and its derivatives were also discovered in some cases, with acetylfentanyl being the most prevalent after fentanyl.

Metabolite to parent drug ratios for amphetamine to methamphetamine are expected to be roughly 0.1 (10%) if amphetamine is present as metabolite of methamphetamine. The mean ratio yielded in this data was 0.14, which is roughly what is expected. In this data, amphetamine:methamphetamine ratios ranged from 0.01 to 5.0. In 47 cases the ratio was > 0.14, in 20 cases the ratio was > 0.5, and in one case the ratio was > 1.0. This indicates that there were some cases that had combined usage of amphetamine along with methamphetamine.

In order to compare the data provided by the NYC-OCME for postmortem methamphetamine casework, several articles and government statistics were used. Many of these articles are from other countries due to the fact that few postmortem research articles have been published pertaining to cases in the United States. Countries include Australia, Iran, Thailand, and Saudi Arabia. Research regarding postmortem methamphetamine data typically consists of the average age and most common sex seen in the casework. In most studies from the previously listed counties, the average age typically ranges from 32-34 years old, however the closest average that was consistent with this data was 37.47 which was observed in casework from Tehran, Iran (Paknahad et al., 2021). Males were also the most common sex in all casework studied, typically accounting for over 70% of each countries casework. The high prevalence of opioids seen in this study, specifically fentanyl, is consistent with data observed by the Substance Abuse and Mental Health Services Administration (2019), Twillman et

al. (2020), and Jones et al. (2020b). The emerging threat reports published by the DEA in 2018 and 2019 highlighted the most common fentanyl and fentanyl related compounds identified throughout the year. Similar to the DEA data, the 2018 and 2019 NYC-OCME casework identified acetylfentanyl as the second most common type of fentanyl derivative following fentanyl. Aside from opioids, another commonly detected class of drugs was CNS depressants, specifically benzodiazepines which was also observed in postmortem methamphetamine casework in Australia, where they observed 41% of the cases having benzodiazepines (Kaye et al., 2008). The use of cocaine in combination with methamphetamine in homicides was also observed in research by Molina & Hargrove (2017) conducted in Texas, however, they did not use concentration values to compare statistical significance. Our data showed, when observing all manners of death associated with methamphetamine and cocaine together, there was a large difference in methamphetamine concentration compared to that of cocaine, suggesting a more intense exposure to methamphetamine than to cocaine. However, when observing the two drugs specifically in the case of homicides, it was seen that cocaine concentrations were comparable to methamphetamine.

Median postmortem methamphetamine and amphetamine concentrations from Australia were 0.2 mg/L and 0.07 mg/L, respectively (Kaye et al., 2008). This is similar to the median concentrations obtained from this NYC-OCME casework, in which the median methamphetamine and amphetamine concentrations were 0.21 mg/L and 0.1 mg/L, respectively. In Saudi Arabia, median methamphetamine death concentrations were split into three groups: methamphetamine only, methamphetamine in combination with another drug, and non-methamphetamine related with values of 0.527 mg/L, 0.161 mg/L, and 0.130 mg/L, respectively (Al-Asmari, 2021). The median methamphetamine concentration obtained in combination with other drugs is similar to that of the NYC-OCME multi-drug related deaths, where a concentration of 0.135 mg/L was observed. However, methamphetamine-only related deaths and non-drug related deaths were not similar to those discovered by Al-Asmari, having higher concentrations in NYC-OCME, of 1.7 mg/L and 0.345 mg/L, respectively.

In this study, several different components of data analysis were performed that were not observed in other literature regarding postmortem methamphetamine use. This is mainly due to the fact that data originated from NYC, thus allowing other basic demographics to be explored. This includes ethnicity data and the boroughs that individuals consuming methamphetamine were coming from. The exploration of fentanyl derivatives was also quite unique to the data, as it has not been

explored in methamphetamine casework previously. Though methamphetamine in combination with cocaine for homicides has been explored for accidental and homicide deaths, the concentration values have not.

5. Conclusion

In summation, the data analysis performed on the NYC-OCME postmortem methamphetamine casework from 2018 and 2019 provided an insightful way to observe trends and patterns correlating to the drug, specifically when comparing this research to published literature. In general, results found in this study were similar to other sources, such as males being more likely to use the drug, as well as the types of drugs found in combination with methamphetamine, such as opioids, cocaine and various benzodiazepines. There are also many aspects of information explored in this study that have not been previously observed, such as comparing the statistical significance of postmortem methamphetamine concentrations by demographics, as well as through different causes of death and combination with other substances. This research can eventually be expanded upon in future studies and more information regarding methamphetamine use can be explored.

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