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Toxicological and pharmacologic sex differences in unintentional or undetermined opioid overdose death

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Abstract

Intro: Understanding sex differences in toxicological etiologies of opioid-related drug overdose death could inform future sex- and gender-specific approaches to prevention and treatment.

Methods: A retrospective review of accidental or undetermined opioid-involved overdose deaths in Rhode Island 2016–2019 was performed using the Rhode Island Department of Health State Unintentional Drug Overdose Reporting System (SUDORS) database. Decedent toxicology data was linked with state Prescription Drug Monitoring Program (PDMP) records.

Results: Of 766 cases in the analytical sample, 568 cases were in men (74.2%) and 198 cases were in women (25.6%). Median age was 40.0 years for males and 42.0 years for females. Statistically significant sex-differences in drug exposures were found. Compared to men, women were more likely have exposure to benzodiazepine, antipsychotic, and antidepressant drug classes and less likely to have fentanyl and alcohol co-exposure. No sex differences were found in cocaine

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Dr. Rachel Wightman contributed to all aspects of the study including design, data acquisition, analysis, and manuscript creation.
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Dr. Benjamin Hallowell contributed to data extraction, linkage to PDMP, data transfer, interpretation, and manuscript editing and review.
Maxwell Krieger contributed to data extraction, transfer, and facilitated data analysis, manuscript editing and review.
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and amphetamine exposure. Female decedents were more likely than male decedents to have a prescription for benzodiazepines or opioids in the 30 days before death (40% vs 21%). The proportion of decedents with a benzodiazepine on post-mortem toxicology testing in combination with a benzodiazepine prescription ($p<0.001$) or an opioid prescription ($p=0.005$) was over two times higher in women than men.

Conclusion: Higher rates of controlled substance prescription prior to death and prescription drug co-exposures suggest that female opioid-involved drug overdose decedents are often in contact with the health care system immediately preceding their death, presenting the opportunity to create patient-centric approaches for prevention, harm reduction, and substance use treatment.

Keywords

sex differences; opioid overdose; post-mortem toxicology; overdose mortality

1.0 Intro:

The path to opioid use and opioid use disorder is often different for women compared to men. Women with opioid dependence are more likely than men to be exposed to opioids through the health care system and to be prescribed an opioid medication for chronic pain (Back et al., 2011; Cicero et al., 2009; Hirschtritt et al., 2018). Contributing factors also include the finding that women with opioid dependence have higher rates of medical and other psychiatric comorbidity, demonstrate greater illness severity and functional impairment, and have less satisfactory treatment outcomes than men (Bawor et al., 2015; Grella et al., 2009; McHugh et al., 2018). In both human studies and animal models, females are more likely to have a more rapid evolution from opioid initiation to development of compulsive use and dependence, and are more vulnerable to return to use following a period of abstinence (Becker and Hu, 2008; Hernandez-Avila et al., 2004; Zilberman et al., 2003).

Additionally, there are important sex-based differences in prescribing trends for controlled substances in the United States. For example, women are more likely to be co-prescribed with opioids medications such as benzodiazepines that place them at increased risk for unintentional polydrug overdose (Hwang et al., 2016). Although men have higher rates of illicit drug use and opioid-related deaths in the United States when compared to women (Substance Abuse and Mental Health Services Administration, 2020), the rate of increase in overdose deaths is similar among women and men in recent years (National Institute of Drug Abuse, 2020; VanHouten, 2019). From 1999 to 2019, the rate of age-adjusted drug overdose death rates increased by over 350% for both men and women (Hedegaard et al., 2020). Specifically among women aged 30–64 years in the United States between 1999–2018, there was notable increase in deaths involving synthetic opioids (1,643%), heroin (915%), and benzodiazepines (830%) (VanHouten, 2019).

Despite documented differences in all phases of drug dependence including drug acquisition, escalation of use, withdrawal, recurrence of use, and treatment response, most national and local initiatives to address the opioid overdose crisis fail to take into account these sex and gender differences (Mazure and Fiellin, 2018). According to the NIH, sex as a biological variable (i.e., male, female, intersex) is an important determinant in research

design, analysis and reporting data (Arnegard et al, 2020). Previous efforts to evaluate comparative risk for overdose mortality in women compared to men have focused on sex differences based on geography (Hedegaard et al., 2019a), or prescription history including study of the presence or absence of prescribed opioids (Khodneva et al., 2019), and those with opioid prescriptions for chronic, non-cancer pain (Kaplovitch et al., 2015). However, to our knowledge, there has not been a detailed evaluation of sex differences in toxicological drivers of unintentional opioid-involved drug overdose death, specifically what drugs were present in the body at the time of death with linkage to retrospective prescription data. These data could have meaningful implications to inform opioid prescribing practices and sex and gender-specific approaches to prevention and treatment. In this context, we conducted an analysis of sex-specific toxicologic and pharmacologic differences in drugs found at death in victims of fatal opioid overdose to determine incidence of co-exposure via analysis of post-mortem toxicology testing. Further, decedent toxicology data was linked with the prescription drug monitoring program (PDMP) records to evaluate the association of prescribed benzodiazepines and opioids in opioid-involved drug overdose death.

2.0 Methods:

2.1 Setting and Study Design

We conducted this study in Rhode Island (RI), a state with the 14th highest rate of overdose mortality in 2019 (Center for Disease Control and Prevention, 2021). In RI there is a statewide medical examiner system, which results in uniform toxicology testing procedures and streamlined reporting (PreventOverdoseRI, 2020; Rhode Island Department of Health, 2020). A retrospective review of all accidental or undetermined opioid-involved overdose deaths (aged 15 to 70) occurring in RI from 2016–2019 was performed using data from the RI Department of Health (RIDOH) State Unintentional Drug Overdose Reporting System (SUDORS) database (Department of Health, 2021).

2.2. Data Sources

SUDORS is a Centers of Disease Control (CDC) funded database that contains comprehensive information abstracted from multiple sources, including medical examiner records, death certificates, and law enforcement records (Jiang et al., 2018). Information is abstracted by a team of trained abstractors and entered into SUDORS. Variables are coded in a consistent manner based on a CDC-provided coding manual. Within SUDORS, the term “sex” was used to describe decedents’ sex at the time of death. This variable implies assigned sex based on primary and secondary sex characteristics observed by the medical examiner and any identification records available. Gender identity at the time of death is not available, including whether decedents were gender diverse people (e.g., transgender). As such, when describing sex in this paper, we used man and woman as nouns and male and female as adjectives to represent sex.

The RI’s SUDORS database includes all cases for which: (1) the death was pronounced in RI; (2) the Office of the State Medical Examiner (OSME) determined the manner of death to be either ‘Accident’ or ‘Undetermined’; and (3), an opioid was listed as the primary cause of death or a significant contributing factor. The forensic toxicology lab at

the OSME has a standard testing protocol for analyzing casework. Preliminary drug testing is performed on whole blood specimens using the ELISA (enzyme-linked immunosorbent assay) technique. Drug classes tested include: alcohol, amphetamines, anticonvulsants, antidepressants, antipsychotics, barbiturates, benzodiazepines, cannabis (cannabinoids), cocaine, muscle relaxants, and opioids.

Presumptive positive results from ELISA testing were subject to confirmatory testing (i.e., gas chromatography/mass spectrometry (GC-MS) or liquid chromatography/ tandem mass spectrometry), which was also performed on a whole blood specimen. Reporting limits of detection for opioids of interest to this study were: buprenorphine 0.5 ng/mL, fentanyl 0.1 ng/mL, methadone (25 ng/mL until May 2018, then 5 ng/mL after May 2018). Fentanyl and fentanyl analogues were detected initially via a GC-MS screening method by the RI OSME and then confirmed by an outside laboratory. Naloxone was tested via GC/MS and was reported as positive or negative without quantification. Toxicology testing in SUDORS is reported as positive or negative (i.e., quantitative toxicology data is not available). Cases were excluded if they did not have testing consistent with the OSME standard toxicologic testing protocol defined as missing data or lack of testing in all drug classes.

To obtain an individuals' opioid and benzodiazepine prescription history (excluding buprenorphine) from the RI PDMP for the 30 days preceding death, SUDORS records were linked by RIDOH to OSME data via the OSME case numbers found in SUDORS. Individuals were then linked to the RI PDMP using a unique identifier composed of portions of their last and first name and their date of birth. These data were provided in a separate dataset with the SUDORS unique ID. The RI PDMP database contains all controlled prescriptions dispensed in RI, and prescriptions from the surrounding states of Massachusetts and Connecticut for RI-residents. For this study, data were extracted from SUDORS and the PDMP, and de-identified prior to analysis. Demographic data (e.g., age) were aggregated to prevent the ability to trace the data back to an individual. Based on RIDOH small numbers reporting policy, all data elements and results with numbers less than five not including zero are suppressed. All drugs reported on toxicology testing in SUDORS, whether or not determined by the ME as cause of death, were included.

2.3. Measures and Statistical Analysis

Differences in co-exposures on toxicology testing and PDMP prescription history were evaluated in male and female decedents. Reported variables included drug class, specific opioids including buprenorphine and methadone, fentanyl, fentanyl analogues, novel synthetic opioids, and naloxone. Opioid and benzodiazepine prescriptions (excluding buprenorphine) recorded in the PDMP in the 30 days prior to death were reported. To compare differences, we used the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. We also estimated prevalence ratios, comparing women (numerator) to men (denominator), and 95% confidence intervals by using robust Poisson models. This project was reviewed and deemed exempt status by the RIDOH Institutional Review Board (IRB) and the Lifespan IRB because the analysis did not involve living human subjects.

3.0 Results:

3.1 Description of the Study Population

A total of 871 deaths determined by the OSME as accidental and/or undetermined opioid-involved overdose fatalities occurred in RI between June 2016 and June 2019. A total of 105 (12.06%) cases were excluded because they did not have standard toxicology testing available, leaving a total of 766 cases in the analytic sample. Of the 766 cases, 568 (74.15%) cases were in men and 198 (25.85%) cases were in women. The age distribution by sex is shown in Table 1. The median age was 40.0 years for men and 42.0 years for women (p = 0.212).

3.2 Co-exposure by Drug Class

Co-exposures by drug class on toxicology testing varied between female and male decedents (Table 2). By definition, all deaths in the dataset had an opioid found on toxicology testing. As shown in Table 2, benzodiazepines, antipsychotics, and antidepressants were more common among women compared to men, while alcohol was less common in women versus men (all p-values ≤ 0.001). The average number of drug classes found on toxicology testing was 3.3 for men and 3.7 for women (p = 0.002).

3.3. Type of Opioid Exposure

As shown in Table 3, there were no statistically significant differences in methadone or buprenorphine exposures on toxicology testing by sex. Fentanyl was found on toxicology testing in 75% of cases and fentanyl(s) including fentanyl, fentanyl analogues, and novel synthetic opioids were found on toxicology testing in 78% of cases in the analytical sample. We found statistically significant sex differences in both fentanyl and fentanyl(s) including fentanyl analogues and novel synthetic opioids, with men more likely than women to die with fentanyl(s) on toxicology testing. Naloxone was rarely noted in fatalities (see Table 3).

3.4 Benzodiazepine and Opioid Prescription and Exposure

As shown in Table 4, according to linked PDMP data, female decedents were more likely to have a benzodiazepine prescription within 30 days prior to death compared to male decedents (p < 0.001). A recent opioid prescription was also more common among women than men (p = 0.013). Women were also more likely to have both a benzodiazepine and opioid prescription within 30 days of death (p < 0.001), according to data in the PDMP database. Notably, both the proportion of decedents who had a PDMP benzodiazepine prescription in combination with a benzodiazepine found on post-mortem toxicology testing (p < 0.001), and the proportion of decedents with a PDMP opioid prescription and a benzodiazepine detected on post-mortem toxicology testing (p = 0.005) was over two times higher in women compared to men.

4.0 Discussion:

In this retrospective review of opioid-involved drug fatalities occurring in Rhode Island from 2016–2019, we found significant and distinctive patterns of co-exposures in addition to opioids on post-mortem toxicology testing in women and men. Alcohol and fentanyl

exposure was found more frequently on toxicology testing in male than female decedents. In contrast, benzodiazepines, antipsychotics, and antidepressants were found more often on post-mortem toxicology testing in women compared to men. Recently, the CDC noted an increase in illicit fentanyl deaths with co-exposure to benzodiazepines (32.5%), cocaine (34.0%), or amphetamine (12.1%) (Gladden, 2019). Our data demonstrate similar polysubstance co-exposures, including fentanyl and fentanyl analogues (78% of cases overall), as well as a high prevalence of benzodiazepines and illicit stimulants. Interestingly, there was no sex difference in amphetamine or cocaine exposure. However, exposure to amphetamine in our sample was lower than national reports, but consistent with known regional variation (Hedegaard et al., 2019b).

Prior studies have found that women with substance use disorder have higher mental health and medical comorbidity and that women are more likely to start using drugs in order to self-medicate to reduce symptoms of mental disorders and emotional stress (Becker and Hu, 2008; Jamison et al., 2010). In a study examining individuals who filled an opioid prescription, although women received lower dose opioids, they were more likely to have an antidepressant, benzodiazepine or zolpidem co-prescription (Liang et al., 2016). This parallels our findings that co-exposures to antidepressants and antipsychotics were higher in female compared with male decedents. Sex differences were also noted for benzodiazepine exposure, with women approximately 75% more likely to have a benzodiazepine as a co-exposure found on toxicology testing. Further, of women who died from opioid-involved drug overdose during the study period, approximately 30% had a benzodiazepine prescription dispensed within the last 30 days of the date of death, and 21% had both a benzodiazepine prescription within 30 days and benzodiazepines found on post-mortem toxicology, according to linked multi-state PDMP data. These findings indicate that many women who die of an opioid overdose are touching the health care system and often obtaining benzodiazepines via prescription, which in turn likely contribute to overdose death.

In Rhode Island there has already been active effort to reduce co-prescribing of benzodiazepines and opioids. From 2017 to 2020, the number of people who receive overlapping opioid and benzodiazepine prescriptions decreased by 42%, according to state surveillance data (PreventOverdoseRI, 2021). However, our findings emphasize the continued need for targeted interventions, especially in women, to not only reduce co-prescription of benzodiazepines and opioids, but also counsel women to avoid co-exposure to sedatives and opioids regardless if they are obtained via prescription or the unregulated market. Polysubstance use and polypharmacy are known risk factor for adverse drug events and overdose, especially if multiple drugs affecting the central nervous system are used concurrently (Collett et al., 2016; O'Donnell, 2020; Schneider et al., 2019). Polysubstance use is also linked with poorer mental health in both men and women, including psychological distress, anxiety, and depression (Egan et al., 2013; Jones et al., 2012; Mccabe et al., 2006). A detailed medication reconciliation with a pharmacist or physician at intake could highlight potential medication interactions and provide an opportunity to evaluate the utility of each medication taken, reduce prescription of non-essential medications, and avoid harmful polypharmacy. For patients with combined opioid and benzodiazepine use with physical dependence, abrupt tapering or stopping either medication

could place them at risk for withdrawal. When appropriate, gradual patient-centered tapering strategies can be supported by providers before and during the process by incorporating psychosocial services, providing encouragement, and anticipatory guidance about potential withdrawal syndromes, and emphasizing alternative strategies for managing stress (Soyka, 2017; Lader et al., 2009). In prior research, patients who had a benzodiazepine prescribed by their primary care physician were more likely than those receiving a benzodiazepine prescription from another medical provider to cease or reduce benzodiazepine use, further emphasizing the significance of the provider-patient relationship and trust (Heather et al., 2011). In specific clinical circumstances in which it may be indicated to co-prescribe an opioid and benzodiazepine (such as patients with co-morbid mental illness and chronic pain where alternative therapies are inadequate), co-prescription of naloxone, ongoing assessment of indication, and using the lowest dose needed to achieve clinical effect are valuable harm reduction strategies to consider. Additionally, given the extent of female co-exposure to benzodiazepines, antipsychotics, and antidepressants and previously noted PDMP prescription history, sex-specific strategies targeting pain management, anxiety, and depression in women with opioid use disorder should be explored.

As the opioid overdose epidemic evolves, public health officials and researchers need to take a comprehensive approach to consider how drug use, both illicit and licit, affects groups and individuals differently. Our findings of sex differences in co-exposures found in opioid-involved fatalities can be used to inform future efforts to create targeted prevention and treatment approaches.

4.1 Limitations

This study has several limitations. The data sample is limited to overdose surveillance data from only a single state. This limits the external generalizability of the data. Clinical context, for example, individual variance in opioid tolerance, is not available in this de-identified dataset and can limit the ability to interpret the significance of post-mortem toxicology testing results. Toxicology testing presented is qualitative, reported as either positive or negative, and by class, and specific agents other than fentanyl, methadone, and buprenorphine are not detailed. No drug concentrations were available within the dataset. Additionally, cases were excluded that did not have complete toxicology testing. There is a chance that these excluded cases could have different characteristics than included cases. Unfortunately, accurate race and ethnicity data was not available in the extracted dataset. These are important data elements to include in future study. Prescriptions filled in the 18 states not queried by the PDMP search could be missed.

PDMP data linked in this study only provides information on whether an opioid or benzodiazepine prescription is documented within 30 days of death. Detailed descriptions of the specific benzodiazepine or opioid prescription present were not queried. Future study will be needed to better delineate if decedents were taking the specific medication they were prescribed at the time of death. Additionally, these data are limited to the biological variable of sex. Gender identity differences could not be assessed, as this data element is not reported within SUDORS. Future studies will need to consider both sex and gender when evaluating for differences in opioid use, opioid use disorder, and overdose risk.

4.2 Conclusion

In this three-year, population-based study, benzodiazepines, antipsychotics, and antidepressants co-exposures were more common among female decedents, while alcohol and fentanyl co-exposures were more common in male decedents. Higher rates of controlled substance prescription prior to death and prescription drug co-exposures suggest that female opioid-involved drug overdose decedents are often in contact with the health care system in the 30 days prior to death, presenting the opportunity to create patient-centric approaches to prevention, harm reduction, and substance use treatment.

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Highlights:

- Women had higher benzodiazepine, antipsychotic, and antidepressant exposure.
- Men were more likely to have alcohol and fentanyl exposure.
- No sex differences were found in cocaine and amphetamine exposure.
- Women were more likely to be prescribed a benzodiazepine or opioid prior to death.
- 30% of women had a benzodiazepine prescription dispensed within 30 days of death.

Table 1.

Demographics of opioid-involved accidental or undetermined overdose fatalities in Rhode Island, June 2016–June 2019.

	Men		Women		
	Count	**Percent**	**Count**	**Percent**	***p*-value**
Total Deaths	568	74.15%	198	25.85%	N/A
Age (years)					0.443
15–24	36	6.34%	12	6.06%	
25–34	161	28.35%	47	23.74%	
35–44	156	27.46%	51	25.76%	
45–54	116	20.42%	42	21.21%	
55–64	83	14.61%	41	20.71%	
65+	16	2.82%	5	2.53%	
Mean (SD)	41.3 (12.1) years		42.9 (12.5) years		0.445
Median (IQR)	40.0 (31.5–50.5) years		42.0 (33.0–54.0) years		0.202

Table 2.

Drug classes found on toxicology testing among opioid-involved accidental and undetermined overdose fatalities in Rhode Island, June 2016–June 2019.

	Men (n=568)		Women (n=198)		Prevalence Ratio* (95%CI)	*p*-value
Drug Class	**Count**	**Percent**	**Count**	**Percent**		
Opioids	568	100%	198	100%		N/A
Alcohols	213	38%	40	20%	0.56 (0.41 – 0.76)	<0.001
Benzodiazepines	121	21%	74	37%	1.83 (1.38 – 2.43)	<0.001
Cocaine	237	42%	76	38%	0.80 (0.64 – 1.01)	0.060
Amphetamines	51	9%	17	9%	1.26 (0.69 – 2.29)	0.449
Antipsychotics	34	6%	29	15%	2.29 (1.38 – 3.81)	0.001
Antidepressants	100	18%	75	38%	2.07 (1.55 – 2.77)	<0.001
Cannabinoids	164	29%	45	23%	0.76 (0.57 – 1.02)	0.096

* Prevalence ratios compare women (numerator) to men (denominator)

Table 3.

Fentanyl, methadone, buprenorphine, and naloxone found on toxicology testing among opioid-involved accidental and undetermined overdose fatalities in Rhode Island, June 2016–June 2019.

	Men (n=568)		Women (n=198)		Prevalence Ratio (95%CI)	*p*-value
Individual Drugs	**Count**	**Percent**	**Count**	**Percent**		
Fentanyl	444	78%	130	66%	0.84 (0.75, 0.94)	0.002
Fentanyl(s) including fentanyl analogues and novel synthetic opioids	461	81%	138	70%	0.88 (0.78, 1.00)	0.044
Methadone	62	11%	30	15%	1.42 (0.94, 2.15)	0.096
Buprenorphine	37	7%	18	9%	1.56 (0.89, 2.72)	0.121
Naloxone	<5	*	8	4%	*	*

* indicates a suppressed value due to the Rhode Island Department of Health small numbers policy

Table 4.

Prescribing history of opioids (excluding buprenorphine) and benzodiazepines 30 days prior to death among fatal opioid-involved overdose decedents in Rhode Island, June 2016–June 2019.

Men (n=568)			Women (n=198)		Prevalence Ratio (95%CI)	p-value
Dispensed prescription in PDMP within 30 days of death	**Count**	**Percent**	**Count**	**Percent**		
Benzodiazepine prescription	74	13%	60	30%	2.19 (1.57, 3.06)	<0.001
Opioid prescription	67	12%	42	21%	1.75 (1.13, 2.73)	0.013
Benzodiazepine AND opioid prescription	24	4%	23	12%	2.75 (1.59, 4.76)	<0.001
Benzodiazepine prescription and benzodiazepine found on post-mortem toxicology testing	44	8%	41	21%	2.67 (1.80, 3.96)	<0.001
Opioid prescription and benzodiazepine on post-mortem toxicology testing	22	4%	18	9%	2.34 (1.29, 4.28)	0.005