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Concordance between controlled substance receipt and post-mortem toxicology in opioid-detected overdose deaths: A statewide analysis

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ABSTRACT

Background: Opioid overdoses are a leading cause of preventable death in the United States. There is limited research linking decedents' receipt of controlled substances and presence of controlled substances on post-mortem toxicology (PMT).

Methods: We linked data on opioid-detected deaths in Connecticut between May 3, 2016, and December 31, 2017 from the Office of the Chief Medical Examiner, Department of Consumer Protection, and Department of Mental Health and Addiction Services. Exposure was defined as receipt of an opioid or benzodiazepine prescription within 90 days prior to death. Our primary outcome was concordance between medication received and metabolites in PMT.

Results: Our analysis included 1412 opioid-detected overdose deaths. 47 % received an opioid or benzodiazepine 90 days prior to death; 36 % received an opioid and 27 % received a benzodiazepine. Concordance between receipt of an opioid or benzodiazepine and its presence in PMT was observed in 30 % of opioid-detected deaths. Concordance with an opioid was present in 17 % of opioid-detected deaths and concordance with a benzodiazepine was present in 21 % of opioid-detected deaths. Receipt of an opioid or benzodiazepine and concordance with PMT were less common in fentanyl or heroin-detected deaths and more common in pharmaceutical opioid-detected deaths.

Discussion: Our results suggest medically supplied opioids and benzodiazepines potentially contributed to a substantial number, though minority, of opioid-detected deaths during the study period. Efforts to reduce opioid and benzodiazepine prescribing may reduce risk of opioid-detected deaths in this group, but other approaches will be needed to address most opioid-detected deaths that involved non-pharmaceutical opioids.

1. Background

In the United States, opioid overdose deaths have tripled since 2010 and have become a leading cause of preventable death (Rudd et al., 2016). In the 12-month period ending in April 2021, opioids were implicated in over 75,000 overdose deaths (National Center for Health Statistics, 2021). Despite increasing public health and policy focus on this issue, following a slight decrease in 2018, opioid overdose deaths continue to increase (Ahmad et al., 2021). Although the causes driving ongoing increases are multiple and debated, including a changing illicit drug supply (Ciccarone, 2017, 2019; O'Donnell et al., 2018; Park et al., 2021) and structural factors (Monnat et al., 2019), some consider the

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surge in opioid analgesic prescribing from the mid-1990s until the early-2010s as a component driver of the initial overdose crisis. The increase in opioid prescribing was mirrored by an increase in benzodiazepine prescribing over a similar time period, which has also contributed to rising overdose deaths (Bachhuber et al., 2016; Gladden et al., 2019).

As a class of drugs, opioids encompass both Food and Drug Administration (FDA)-regulated medications produced by pharmaceutical companies and distributed via pharmacies and substances produced and distributed through illegal and unregulated markets, such as heroin and illicitly manufactured fentanyl and its analogs. Use of opioids from either supply chain carries the risk of fatal overdose, and toxicological analyses of opioid-detected deaths during the current crisis regularly identify both pharmaceutically and non-pharmaceutically produced opioids (Seth et al., 2018; Walley et al., 2019). In addition, benzodiazepines, also available both via prescription and via illegal and unregulated markets can contribute to opioid-detected overdose deaths (Gladden et al., 2019). While originating as prescriptions from medical professionals, pharmaceutically produced opioids and benzodiazepines also can enter the drug market through trading, selling or sharing (Drug Enforcement Administration, 2020). Therefore, when identified in toxicological analysis of a fatal overdose, a pharmaceutical opioid or benzodiazepine could have originated either in a prescription written to the decedent or diverted to the illegal drug market.

Previous research has shown an ecological association at the state and county levels between per-capita opioid prescribing and fatal opioid overdose incidence (Friedman et al., 2019; Hadland et al., 2019). Other research has shown that individuals continue to receive opioid prescriptions following a non-fatal opioid overdose (Larochelle et al., 2016) and that $>$ 25 % of individuals with a fatal opioid overdose received a prescription for an opioid in the three months prior to the overdose (Lin et al., 2019). There is limited research attempting to link individual level data of a decedent's history of prescribed controlled substances (inclusive of opioids, benzodiazepines, and other substances) and toxicological results on autopsy (Rose et al., 2018; Slavova et al., 2017).

To address this gap in knowledge, our objective was to examine an individual-level dataset linking multiple sources of Connecticut data from 2016 to 2017 (Becker et al., 2021) in order to identify the proportion of post-mortem toxicology (PMT) results of opioid-detected overdose deaths that contain an opioid or benzodiazepine, or their metabolites, prescribed to the decedent. Connecticut experienced over 2000 opioid overdose deaths during this time, the tenth highest per capita rate of opioid overdose deaths in the country (Rhee et al., 2019; Scholl et al., 2018).

2. Methods

To examine prescriptions received prior to opioid-detected overdose deaths and their concordance with PMT, we accessed three sets of data collected by state agencies in Connecticut. These included records of opioid-detected overdose deaths from the Connecticut Office of the Chief Medical Examiner (OCME), substance use treatment data from the Connecticut Department of Mental Health and Addiction Services (DMHAS), and controlled substance receipt data from the Connecticut Prescription Monitoring and Reporting System (CPMRS) run by the Connecticut Department of Consumer Protection (DCP). The study included all individuals with an OCME-investigated accidental or undetermined opioid-detected overdose death in Connecticut between May 3, 2016 and December 31, 2017.

2.1. Data sources

For this study we used data from the OCME investigations. In Connecticut, all sudden, unexpected, or unnatural deaths are reported to the OCME for possible investigation, and all OCME death investigations involve toxicological testing when a tissue sample is available (Office of Chief Medical Examiner, 2006). For the current study, we included all accidental or undetermined overdose deaths investigated by the OCME where a quantifiable amount of at least one opioid (or its metabolite) was listed in the toxicology report. We excluded deaths due to intentional poisonings (i.e., suicides, homicides) and deaths involving blunt-force trauma (e.g., falls, motor vehicle accidents), drowning, therapeutic complications, or environmental exposure from the final data set. Deaths due to intentional poisoning were excluded as the context and causes of these deaths likely differ from those of accidental poisonings and were not the focus of our study. OCME data included immediate toxicology results, date of death, date of birth, biological sex, race, and ethnicity. Our team verified the cause and manner of death against source documents (i.e., reports of toxicological testing, autopsy, and investigation) using manual chart review of all opioid-detected deaths. We recorded all substances with a quantifiable amount detected in the PMT.

For this study, data on prescriptions dispensed in Connecticut from CPMRS included name of medication, strength, quantity, and written and fill date for all prescriptions as well as demographic and residential address data used for matching. As methadone dispensing from opioid treatment programs (OTPs) is not captured in CPMRS, we collected methadone dispensing details as reported to the Connecticut DMHAS. DMHAS treatment data are recorded as individual continuous episodes of care and include all addiction treatment episodes including inpatient treatment (detoxification, long-term residential treatment) and outpatient treatment (including methadone from opioid treatment programs). The DMHAS data set also includes treatment recipients' identifying information (name, age) and demographic characteristics for use in matching and linkage.

For our analysis, we linked the three datasets included (OCME, CPMRS, DMHAS) at the individual level. The merging and linking of these datasets was carried out as part of the larger effort to combine statewide administrative datasets. The details on the data source identification, access, merging, and linkage are described in detail elsewhere (Becker et al., 2021). Briefly, to create a per-person profile of exposures and outcomes, we used a public domain software program (The Link King V9, www.the-link-king.com) that integrates both probabilistic and deterministic matching algorithms to identify and match individual records across the three agencies using all available demographic identifiers and geographic information, such as name, gender, birth date, social security number, residential address, and zip code. Previous literature has found that this software can achieve a high degree of linking accuracy with sensitivity and positive predictive values greater than 90 % (Campbell et al., 2006). We included all decedents in our final dataset even if no CPMRS or DMHAS records were linked under the assumption that some number of decedents would not have touched these systems.

2.2. Exposure to prescribed controlled substances

The primary exposure of interest was recent receipt of a prescribed opioid or benzodiazepine defined as a filled opioid or benzodiazepine prescription, as documented in CPMRS, or a receipt of methadone from an OTP, as documented by DMHAS, in the 90 days prior to an opioid-detected death. The 90-day time period was used as a measure of recency of a filled prescription or medication receipt. This time period for recency was consistent with previously published literature used for this purpose (Lin et al., 2019; Nechuta et al., 2018), though a range of time windows have been used in other studies (Hall et al., 2008; Lev et al., 2016; Mercado et al., 2018; Nechuta et al., 2018; Paulozzi et al., 2009; Slavova et al., 2017; Weimer et al., 2011). From CPMRS data, we included prescriptions covering any period within the 90-day interval preceding death. From DMHAS data, we included methadone treatment episodes during the 90-day period, including those that initiated or ended within 90 days of death. Given the range of time periods used in the previous literature to determine recency of controlled substance

receipt we repeated our analysis using a 60- and 30-day time period as a sensitivity analysis.

Different medications were categorized by substance (e.g., oxycodone, hydrocodone, buprenorphine, alprazolam, etc.), drug class (opioid vs. benzodiazepine), and, for opioids, indication (medications for opioid use disorder (MOUD) vs. pain). Individuals were considered to have received MOUD if there was filled prescription for a formulation of buprenorphine indicated solely for the treatment of OUD (e.g., Suboxone, Subutex, Zubsolv) in CPMRS data or a treatment episode for methadone in the DMHAS data. In our classification of MOUD we did not include filled prescriptions for formulations of buprenorphine with an indication for pain (e.g., Belbuca, Butrans). Filled prescriptions for methadone in the CPMRS data were not included as MOUD given federal regulations which would prohibit its use for the treatment of OUD in this context. Of note, CPMRS does not include records of filled prescriptions for naltrexone, an opioid antagonist which is also a form of MOUD, as it is not a controlled substance and therefore it was not included in our analysis.

Finally, to capture the range of exposures, we also calculated mean daily morphine milligram equivalents (MMEs) for each non-MOUD opioid prescription and lorazepam milligram equivalents (LMEs) for each benzodiazepine prescription by multiplying the mean raw daily dose by the relevant conversion factor (Bachhuber et al., 2016; Chouinard et al., 1999; Dasgupta et al., 2021; Dowell et al., 2016). We then calculated the mean daily MME and LME for the 90-day interval preceding death by multiplying the daily MME by the number of days of prescription occurring within the 90-day interval and dividing the product by 90. Thus, if fewer than 90 days' prescription were received, 0 mg was averaged into the mean dose for those days. This method for comparing relative opioid exposure for a fixed observation window was chosen to be consistent with recommendations for calculating daily MME from the US Department of Health and Human Services Office of the Inspector General (Dasgupta et al., 2021; Office of the Inspector General, 2018).

2.3. Prescription-toxicology concordance

As described above, for each opioid-detected death we captured data on presence of any opioid, benzodiazepine, or their metabolites. These substances and metabolites were categorized by drug class (opioid vs. benzodiazepine) and by individual substance. We further classified opioid-detected deaths as those where either fentanyl or heroin was detected and those where a pharmaceutical opioid was detected. Presence of fentanyl, fentanyl analogs, heroin, and their metabolites, including 6-monoacetylmorphine (6-mam) and morphine, were categorized as fentanyl or heroin-detected deaths. The presence of any of the following substances or their metabolites were categorized as pharmaceutical opioid-detected deaths: codeine, hydromorphone, oxymorphone, hydrocodone, oxycodone, methadone, buprenorphine, and tramadol. These subgroups are not exclusive of each other as an opioid-detected death that had both a fentanyl/heroin and a pharmaceutical opioid present on PMT would be included in both subgroups.

Morphine that is present on toxicology from pharmaceutical morphine is indistinguishable from morphine as a heroin metabolite (Barceloux, 2012). There are several methods used in toxicology research that attempt to distinguish the origin of morphine in toxicology results, but none that eliminate the possibility of morphine as a heroin metabolite (Barceloux, 2012; Maas et al., 2018). Given the relatively small numbers of morphine prescriptions and widespread use of heroin, we classified all PMTs with morphine metabolites as heroin-detected deaths. Similarly, although fentanyl is a pharmaceutically produced pain medication, the number of fentanyl prescriptions is small and non-medical fentanyl use widespread (O'Donnell et al., 2018, 2017), so we classified all PMTs with fentanyl (including fentanyl metabolite or fentanyl analog) as likely due to illicitly manufactured fentanyl. Given the lack of specificity in the relationship between benzodiazepine parent compounds and metabolites (Mandrioli et al., 2008), we did not attempt to draw inferences on specific benzodiazepine use by the presence of certain metabolites.

Concordance was determined as agreement between the specific opioid or any benzodiazepine prescribed in the 90 days prior to death and a matched substance or metabolite identified on post-mortem toxicology.

2.4. Analysis

We performed descriptive analysis of opioid and benzodiazepine receipt, opioid and benzodiazepine presence in PMT, and concordance between prescription receipt and toxicology for all accidental and undetermined opioid-detected deaths. We calculated the proportion of all decedents with specific prescription exposures and toxicology outcomes as described above. We also conducted bivariate analyses of demographic differences across these groups, testing for statistically significant differences using chi-squared or t-test where appropriate.

2.5. Privacy protection/IRB review

Our study was reviewed and approved by DMHAS and Yale University IRBs. Memoranda of Understanding and Data Use Agreements were maintained for use of DMHAS, DCP, and DMHAS data and, data safety guidelines specified by participating agencies were adhered to.

3. Results

We identified 1412 opioid-detected overdose deaths in Connecticut between May 3, 2016 and December 31, 2017 that were investigated by the OCME. Most decedents were male (74 %) and non-Hispanic White (80 %); average age was 42 (SD ± 12) years. We provide detailed demographics for all included opioid-detected deaths and demographics of different subgroups in Table 1. Following data linkage, we identified 844 decedents in the CPMRS dataset, and 868 decedents had any treatment episode identified in the DMHAS treatment episode data set. Output from our linkage software reported highest possible likelihood of accurate linkage between OCME and DMHAS data sets was achieved for 94.6 % decedents and between OCME and CPMRS data sets was achieved for 92.4 % decedents.

Based on toxicology results from OCME investigations of all opioid-detected overdose deaths, 1193 (84.5 %) were fentanyl or heroin-involved (931 (65.9 %) fentanyl-involved and 759 (53.8 %) heroin-involved) and 603 (42.7 %) were pharmaceutical opioid-detected. A total of 523 (37.0 %) opioid-detected deaths also had a benzodiazepine present on PMT. The presence of different opioids and metabolites in PMT results is reported in Tables 2–4. As noted above, we did not report out presence of individual benzodiazepine types in line with OCME practices.

Of this cohort, 661 decedents (46.8 %) received either an opioid or benzodiazepine in the 90 days prior to death: 613 (43.4 %) filled an opioid or benzodiazepine prescription and 92 (6.5 %) had any recorded methadone-based treatment episode. By medication class, 504 (35.7 %) received an opioid, 380 (26.9 %) received a benzodiazepine, and 223 (15.8 %) received both an opioid and a benzodiazepine. Combining data for buprenorphine receipt and methadone treatment episodes, a total of 196 (13.9 %) decedents received MOUD in the 90 days prior to death. Complete results on prescription receipt prior to death, broken down medication class, substance, and indication, are presented in Fig. 1 and Tables 2–4. Among decedents who received an opioid prescription, excluding MOUD, the median daily MME over the 90-day interval was 6.8 (IQR: 1.60, 57.93). For decedents who received a benzodiazepine prescription, the median daily LME in the 90-day interval was 2.3 (IQR: 0.8, 5.6).

We observed concordance between PMT and an opioid exposure in 242 (17.1 %) decedents, PMT and a benzodiazepine exposure in 293

Table 1
Demographics of all opioid-detected deaths investigated by Office of Chief Medical Examiner (OCME) in Connecticut from May 2016 to December 2017.

	All opioid-detected deaths	Fentanyl or heroin-detected death[1]	Pharmaceutical opioid-detected death[2]	Receipt of opioid or benzodiazpine in prior 90 days	Concordance between post-mortem toxicology and receipt of opioid or benzodiazepine in prior 90 days
N (% of all opioid-involved deaths)	N = 1412 (100 %)	N = 1193 (84.4 %)	N = 603 (42.6 %)	N = 661 (46.8 %)	N = 430 (30.4 %)
Age (mean, SD)	42.1 (± 12.2)	41.3 (± 12.0)	44.2(± 12.2)	44.4 (± 11.9)	45.2 (± 11.8)
Sex (% male)	73.8 %	77.6 %	65.2 %	65.7 %	62.6 %
Race and ethnicity					
Non-Hispanic, White	79.6 %	78.8 %	83.8 %	84.9 %	87.4 %
Non-Hispanic, Black	7.2 %	7.5 %	5.6 %	5.3 %	4.4 %
Hispanic	11.3 %	11.9 %	9.3 %	7.7 %	6.3 %
Other	1.9 %	1.8 %	1.3 %	2.1 %	1.9 %

[1] – fentanyl or heroin-detected deaths include deaths with post-mortem toxicology containing fentanyl, fentanyl analogs, heroin, or heroin metabolites.
[2] – pharmaceutical opioid-detected deaths include deaths with post-mortem toxicology containing opioids or metabolites including codeine, hydromorphone, oxymorphone, hydrocodone, oxycodone, methadone, buprenorphine, or tramadol.

Table 2
Opioid and benzodiazepine receipt and concordance with post-mortem toxicology (PMT) in opioid-detected deaths in Connecticut, May 2016 to December 2017 (N = 1412).

	Present in PMT	% of all opioid-detected deaths	Receipt in prior 90 days	% of all opioid-detected deaths	Receipt and present in PMT	% of all opioid-detected deaths
Opioids (all)	1412	100 %	504	36 %	242	17 %
Non-MOUD	1314	93 %	347	25 %	154	11 %
oxycodone	166	12 %	213	15 %	95	7 %
oxymorphone	102	7 %	5	0.4 %	3	0.2 %
hydrocodone	32	2 %	74	5 %	12	1 %
hydromorphone	52	4 %	25	2 %	11	1 %
fentanyl	931	66 %	17	1 %	12	1 %
morphine	744	53 %	24	2 %	21	1 %
MOUD	191	14 %	196	14 %	93	7 %
buprenorphine	37	3 %	96	7 %	22	2 %
methadone (Rx)[1]	156	11 %	9	0.6 %	4	0.3 %
methadone (OTP)[2]	156	11 %	92	7 %	65	5 %
methadone (all)	156	11 %	101	7 %	69	5 %
Benzodiazepines	523	37 %	380	27 %	293	21 %
alprazolam	NA[3]		162	11 %	120[4]	9 %
clonazepam	NA[3]		142	10 %	118[4]	8 %
diazepam	NA[3]		68	5 %	59[4]	4 %
lorazepam	NA[3]		52	4 %	37[4]	3 %

[1] – includes methadone prescriptions recorded in CT Prescription Monitoring and Reporting System (CPMRS).
[2] – includes methadone treatment episodes recorded in data from CT Department of Mental Health and Addiction Services (DMHAS).
[3] – CT Office of Chief Medical Examiner does not report out benzodiazepine metabolites on post-mortem toxicology.
[4] – reflects concordance of presence of any benzodiazepine on PMT and receipt of specific benzodiazepine.

(20.8 %) decedents, and PMT and either an opioid or benzodiazepine exposure in 430 (30.5 %) decedents. In the subgroup of fentanyl or heroin-detected deaths, which could also involve a pharmaceutical opioid or benzodiazepine, we observed concordance between an opioid or benzodiazepine receipt and PMT in 291 (24.4 %) decedents. In the subgroup of pharmaceutical opioid-detected deaths, we observed concordance between either an opioid or benzodiazepine in 320 (53.1 %) decedents. We present our complete results on observed concordance receipt and PMT by individual opioid and benzodiazepine types in Fig. 1 and Tables 2–4.

The results our sensitivity analysis using 60- and 30-day time periods for receipt of an opioid or benzodiazepine prior to death are presented in Supplementary Table 1. Using these shorter time windows, the percentages of decedents who received an opioid or benzodiazepine prior to their death or had concordance with post-mortem toxicology decreased, but the overall patterns remained consistent to our primary analyses.

4. Discussion

In this analysis of controlled substance receipt for individuals who experienced an opioid-detected overdose death in Connecticut, we found that approximately 1 in 3 decedents received a prescription for an opioid and 1 in 4 for a benzodiazepine in the 90 days prior to their death. In addition, there was concordance in 1 in 6 between receipt of an opioid and the presence of that opioid in PMT and concordance in 1 in 5 between receipt of a benzodiazepine and presence of a benzodiazepine in PMT. Our results suggest that opioids and benzodiazepines prescribed to decedents were potentially a contributing factor in a substantial minority of opioid-detected deaths in Connecticut during this time period. In addition, in the deaths that involved a pharmaceutical opioid, we observed concordance between a filled prescription and PMT in 38 % of these decedents suggesting that diverted pharmaceutical opioids were contributing factors in these deaths.

The 603 pharmaceutical opioid-detected deaths in Connecticut we observed during this time period, and the 242 who had concordance on post-mortem toxicology with recent opioid receipt, highlight the continued need for efforts focused on safe opioid prescribing. In addition, the 523 opioid-detected deaths that also involved benzodiazepines and 380 who received a prescription benzodiazepine prior to death highlight the need to also address safe benzodiazepine prescribing in our

Table 3
Opioid and benzodiazepine receipt and concordance with post-mortem toxicology (PMT) in fentanyl or heroin-detected[1] deaths in Connecticut, May 2016 to December 2017 (N = 1193).

	Present in PMT	% of all fentanyl or heroin-detected deaths	Receipt in prior 90 days	% of all fentanyl or heroin-detected deaths	Receipt and present in PMT	% of all fentanyl or heroin-detected deaths
Opioids (all)	1193	100 %	382	32 %	143	12 %
Non-MOUD	1193	100 %	254	21 %	88	7 %
oxycodone	81	7 %	148	12 %	41	3 %
oxymorphone	44	4 %	3	0.3 %	1	0.1 %
hydrocodone	14	1 %	56	5 %	4	0.3 %
hydromorphone	40	3 %	19	2 %	8	0.7 %
fentanyl	931	78 %	13	1 %	12	1 %
morphine	744	62 %	22	2 %	21	2 %
MOUD	99	8 %	158	13 %	59	5 %
buprenorphine	19	2 %	84	7 %	14	1 %
methadone (Rx)[2]	82	7 %	7	0.6 %	2	0.2 %
methadone (OTP)[3]	82	7 %	68	6 %	42	4 %
methadone (all)	82	7 %	75	6 %	44	4 %
Benzodiazepines	398	33 %	269	23 %	205	17 %
alprazolam	NA[4]		113	9 %	82[5]	7 %
clonazepam	NA[4]		103	9 %	87[5]	7 %
diazepam	NA[4]		47	4 %	40[5]	3 %
lorazepam	NA[4]		35	3 %	26[5]	2 %

1 – includes presence of fentanyl, fentanyl analogs, heroin, 6-mononacetylmorphine, morphine on PMT.
2 – includes methadone prescriptions recorded in CT Prescription Monitoring and Reporting System (CPMRS).
3 – includes methadone treatment episodes recorded in data from CT Department of Mental Health and Addiction Services (DMHAS).
4 – CT Office of Chief Medical Examiner does not report out benzodiazepine metabolites on post-mortem toxicology.
5 – reflects concordance of presence of any benzodiazepine on PMT and receipt of specific benzodiazepine.

Table 4
Opioid and benzodiazepine receipt and concordance with post-mortem toxicology (PMT) in pharmaceutical opioid-detected[1] deaths in Connecticut, May 2016 to December 2017 (N = 603).

	Present in PMT	% of all pharmaceutical opioid-detected deaths	Receipt in prior 90 days	% of all pharmaceutical opioid-detected deaths	Receipt and present in PMT	% of all pharmaceutical opioid-detected deaths
Opioids (all)	603	100 %	319	53 %	232	38 %
Non-MOUD	518	86 %	226	37 %	144	24 %
oxycodone	166	28 %	154	26 %	95	16 %
oxymorphone	102	17 %	5	1 %	3	0.5 %
hydrocodone	32	5 %	41	7 %	12	2 %
hydromorphone	52	9 %	17	3 %	11	2 %
fentanyl	235	39 %	12	2 %	7	1 %
morphine	335	56 %	18	3 %	16	3 %
MOUD	191	32 %	118	20 %	93	15 %
buprenorphine	37	6 %	40	7 %	22	4 %
methadone (Rx)[2]	156	26 %	5	0.8 %	4	0.7 %
methadone (OTP)[3]	156	26 %	74	12 %	65	11 %
methadone (all)	156	26 %	79	13 %	69	11 %
Benzodiazepines	305	51 %	231	38 %	186	31 %
alprazolam	NA[4]		95	16 %	75[5]	12 %
clonazepam	NA[4]		83	14 %	70[5]	12 %
diazepam	NA[4]		46	8 %	41[5]	7 %
lorazepam	NA[4]		36	6 %	26[5]	4 %

1 – includes presence of oxycodone, oxymorphone, hydrocodone, hydromorphone, buprenorphine, or methadone on PMT.
2 – includes methadone prescriptions recorded in CT Prescription Monitoring and Reporting System (CPMRS).
3 – includes methadone treatment episodes recorded in data from CT Department of Mental Health and Addiction Services (DMHAS).
4 – CT Office of Chief Medical Examiner does not report out benzodiazepine metabolites on post-mortem toxicology.
5 – reflects concordance of presence of any benzodiazepine on PMT and receipt of specific benzodiazepine.

efforts to reduce opioid overdose deaths. Efforts to raise awareness of safe opioid and benzodiazepine prescribing practices could have potentially reduced the risk of overdose in these decedents, including the impact the quantity of diverted pharmaceutical opioids and benzodiazepines in the community, which continue to have a significant role (Wang et al., 2014). Although not observable in our study, increased safe opioid and benzodiazepine prescribing can also reduce initial exposure to pharmaceutical opioids and benzodiazepines, which in some individuals can evolve into use of non-pharmaceutical opioids and increasing risk of opioid overdose. Our results also highlight that all interactions with a prescriber leading to receipt of a controlled substance prescription present an opportunity for evaluating risk of overdose, interventions to reduce that risk, such as provision of naloxone, and, for those identified with OUD, initiation of or referral to treatment. Strategies to identify when individuals at risk of overdose engage in medical care and use those opportunities to educate on harm reduction and engage in OUD treatment engagement are needed (Larochelle et al., 2019).

Importantly, we also observed a discrepancy between the proportion of decedents who received an opioid prescription prior to their death and the proportion with PMT concordance. These decedents filled a prescription for an opioid in the 90 days prior to their death that was not

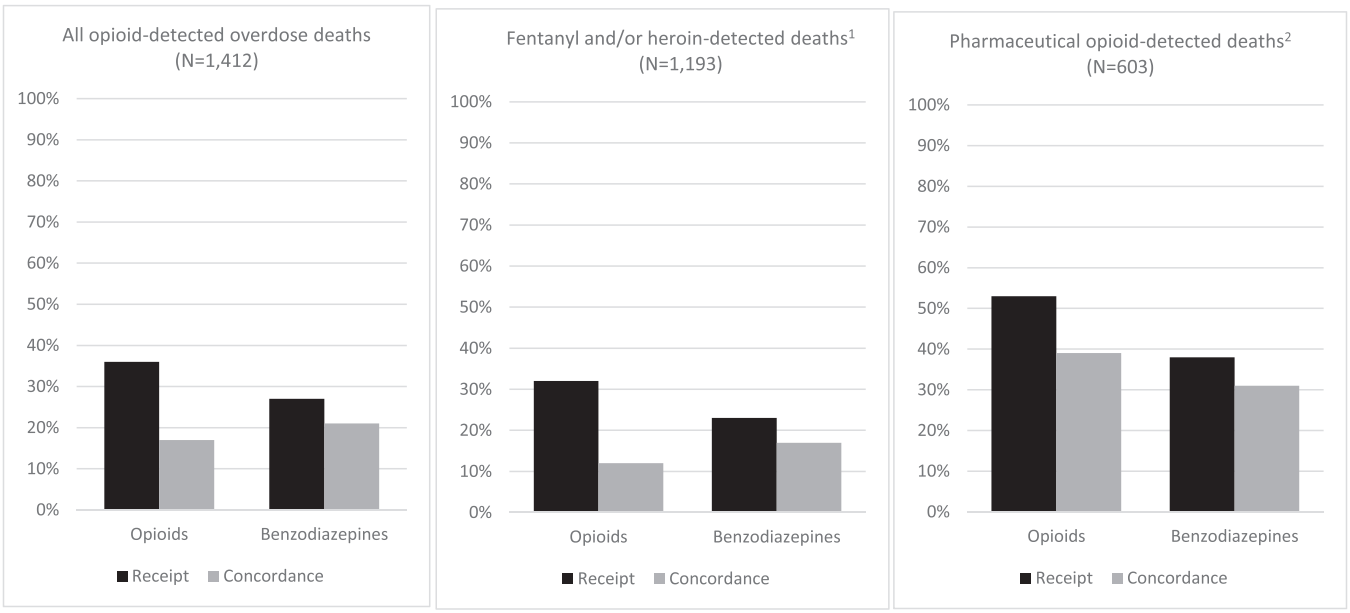

Fig. 1. Opioid and benzodiazepine receipt and concordance with post-mortem toxicology in opioid-detected deaths in Connecticut, May 2016 to December 2017. 1 – fentanyl or heroin-detected deaths include deaths with post-mortem toxicology containing fentanyl, fentanyl analogs, heroin, or heroin metabolites. 2 – pharmaceutical opioid-detected deaths include deaths with post-mortem toxicology containing opioids or metabolites including codeine, hydromorphone, oxymorphone, hydrocodone, oxycodone, methadone, buprenorphine, or tramadol.

present in PMT. Our data cannot speak to what circumstances drove overdose risk in this population, but further exploration of discontinuation of long-term prescription or possible diversion is warranted. Also, our findings do not address the broader consequences of efforts to reduce opioid and benzodiazepine prescribing, especially the outcomes of individuals who experienced discontinuation of long-term opioids who did not experience a fatal overdose. Further research to elucidate the outcomes, including possible benefits and risks, associated with opioid discontinuation is crucial.

Finally, it is also important to note, that a minority of opioid-detected deaths involved pharmaceutical opioids and a low percentage had concordance with a filled prescription. This finding stresses the need for a multi-pronged approach to ameliorating the opioid overdose crisis and the limits of efforts focused on exclusively on safer opioid and benzodiazepine prescribing. Almost 85 % of deaths in this period involved illicitly manufactured fentanyl or heroin, and a majority did not receive an opioid or benzodiazepine prescription in the 90 days prior to their death. Efforts focused on opioid and/or benzodiazepine prescribing would not likely have prevented most of these deaths in the near term. Any of these individuals, as well as those with pharmaceutical opioid-detected deaths, who met criteria for opioid use disorder would have benefited from efforts to increase access to addiction treatment (especially MOUD). Similarly, some of these opioid-detected overdose deaths, both in those with opioid use disorder or intermittent users, may have been avoided with increased access to harm reduction services such as overdose education and naloxone distribution. Methadone and buprenorphine, most often dispensed for the treatment of opioid use disorder, were present on PMT in almost a third of pharmaceutical opioid-detected deaths, largely driven by the presence of methadone.

Our study highlights the usefulness of merging data from different sources in understanding the opioid overdose crisis. Prescription opioid receipt, addiction treatment, and overdose death data in isolation are unable to fully capture the role of different exposures on overdose risk. Linking and merging data, which in many cases are already being gathered, can provide insight into the specific risk and protective factors involved in opioid-related deaths (Larochelle et al., 2018, 2019, 2016; Saloner et al., 2020). It can also be used to provide timely evaluation of interventions and tracking progress in lowering overdose deaths.

Our study adds to previous work using linked administrative data sets which, with one exception, have not linked prescription and treatment data with PMT results. The one previous study linking PMT with prescription history found that a majority of individuals (57 %) with a drug intoxication fatality in 2013–2014 in Kentucky had received a prescribed opioid in the 6 months prior to death, but a smaller proportion (33 %) had an active prescription at time of death (Slavova et al., 2017). The patterns observed from that study highlighted an earlier period in the opioid overdose crisis (2013–2014) when prescription opioids played a larger role in opioid-detected deaths. Since then, illicitly manufactured fentanyl has been responsible for a growing number of opioid overdose deaths and their findings may not be generalizable to other regions of the country with significant demographic differences and different drug market characteristics (Ciccarone, 2017; Murray et al., 2005; Unick et al., 2014). Since 2014, heightened awareness of the dangers of opioids among prescribers, increased scrutiny of opioid prescribing practices, the uptake and mandated use of prescription drug monitoring programs (PDMP), and adoption of guidelines following CDC's published guidelines in 2016 have led to decreased opioid prescribing (Centers for Disease Control and Prevention, 2020; Wilson et al., 2020). Since adoption of these programs generally, and in Connecticut specifically, it is unknown what percentage of decedents of opioid overdoses received a prescription opioid or benzodiazepine in the months leading up to their death and how often those substances may have contributed to the opioid overdose death, based on PMT. Our results demonstrate that following implementation of these monitoring systems, and their mandated use, prescribed opioid and benzodiazepine receipt appear to have decreased, as has been observed in other studies (Lin et al., 2019), yet prescribed opioids and benzodiazepines are still playing a role in overdose deaths.

4.1. Limitations

Our study is not without limitations. The identifying information in CPMRS available to use for data linkage could lead to misclassification of controlled substance exposure, although prior work suggests this is rare (Becker et al., 2021). In addition, controlled substance prescriptions or addiction treatment received outside of Connecticut, which is not

captured in CPMRS and DMHAS data sets, could have led to misclassification of prescription receipt. For our analysis, we relied on PMT as recorded by the Connecticut OCME. This could introduce detection bias based on which deaths were investigated by the OCME, which likely does not capture all overdose deaths in Connecticut during this time. We also excluded deaths due to intentional poisonings (i.e., suicides) as classified by the OCME; it is possible some of these deaths were actually accidental and misclassified by the OCME though we believe this to be rare as suicide adjudication typically rests on clear evidence (e.g., a suicide note). Excluding these deaths means our findings should not inform inferences regarding suicide deaths. In addition, surveillance bias could be introduced as what PMT is performed, classification of PMT, and determination of cause of death are at the discretion of an unblinded OCME. Despite this limitation, use of PMT to characterize opioid-detected deaths is likely an improvement on classification based solely on death certificate data (Hall et al., 2008; Lev et al., 2016; Mercado et al., 2018; Nechuta et al., 2018; Paulozzi et al., 2009; Slavova et al., 2017; Weimer et al., 2011). Finally, we could not account for the source of diverted pharmaceutical opioids in those deaths where there was no record of receipt to that individual, or the role of initial exposure to pharmaceutical opioids on subsequent overdose risk, and therefore cannot address the range of possible effects of safe opioid prescribing efforts.

4.2. Conclusion

Opioid and benzodiazepine prescriptions received within 90 days of death likely played a role in a substantial number, though minority, of opioid-detected deaths in Connecticut during our study period. These results highlight the continued importance of efforts focused on safe opioid and benzodiazepine prescribing, but also the limits of these efforts to reduce risk of overdose in most decedents. Our results highlight, especially at this point in the opioid overdose crisis, that multi-pronged efforts are needed to reduce risk of opioid overdose, especially efforts focused on increasing access to OUD treatment, especially MOUD, and harm reduction services, especially naloxone access.

CRediT authorship contribution statement

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Disclosures/Conflict of Interest

The authors have no financial conflicts of interest to disclose.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2023.109788.

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