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Additive Effects of Cointoxicants in Single-Opioid Induced Deaths

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Abstract

A forensic drug database (FDD) was used to capture comprehensive data from all drug-related deaths in West Virginia, with deaths also included from the northern New England states of Maine, Vermont, and New Hampshire. All four states serve predominantly rural populations under two million and all have similar state medical examiner systems that employ statewide uniform death certification policies and practices. This study focused on 1482 single opioid deaths (fentanyl, hydrocodone, methadone, and oxycodone) in the FDD from 2007–2011. We modeled relationships between the opioid concentrations and the presence or absence of the following commonly

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occurring non-opioid cointoxicants: benzodiazepines (alprazolam and diazepam), alcohol, tricyclic antidepressants, selective serotonin reuptake inhibitors, and diphenhydramine. Additional covariates of state, age, body mass index, and sex were included. Results showed that the presence of alcohol, benzodiazepines, and antidepressants were each associated with statistically significant lower concentrations of some but not all of the opioids studied, which may obscure the interpretation of postmortem toxicology results alone. Fentanyl concentrations appeared to be the least associated with the presence or absence of the variables studied, and cointoxicant alcohol appeared to be associated with lower concentrations in opioid concentrations than were most of the other factors in the model studied. These findings underscore the importance of documenting all potential cointoxicants in opioid-related deaths.

Keywords

Forensic pathology; Cointoxicant; Opioid

INTRODUCTION

Many accidental drug-related deaths involve opioid analgesics in combination with multiple cointoxicants. Despite the frequency of these polydrug deaths, there has been no significant large data research into the complex interrelationships among the cointoxicant drugs present (1, 2). The study of these interrelationships is further complicated by differences in how medical examiner systems of varying types and available resources identify and certify drug-related deaths (3). For example, in acute opioid fatalities with cointoxicant benzodiazepines or antidepressants, some medical examiners mention only the opioid on the death certificate (4). This limits the use of death certificate data alone to study population drug use and abuse-related behavioral changes. The National Association of Medical Examiners and American College of Medical Toxicology Expert Panel presented carefully reasoned guidelines that encourage the mention of all cointoxicants on death certificates for drug-related deaths (3). Yet, questions remain about the potential impact of the individual cointoxicant drugs in such deaths.

Cointoxicants often present with opioids in drug-related deaths include benzodiazepines, alcohol, and antidepressants (5–7). Diphenhydramine was also found to be a cointoxicant in almost 6% of West Virginia drug-induced deaths (8). It is well known that alcohol and drugs with central nervous system depressant effects can exert additive or synergistic toxic effects when used in conjunction with opioids (5). However, the relative contribution of these drugs as causes or contributors to death when present as cointoxicants in opioid-induced deaths has not been well characterized.

In addition to potentially differing effects of cointoxicants when combined with opioids, it is also possible that individual opioids might differ in their propensity to cause adverse effects, including death. A cohort analysis by Solomon et al. found that the risk of cardiovascular events, fracture, and overall mortality differed among opioids (9). Oxycodone users were found to have a stronger association with cardiovascular disease (CVD) related death than non-opioid users, and interestingly, female opioid users were found to have a significantly

greater risk for CVD death compared to male opioid users, particularly in females with underlying CVD (10). A systematic review of the comparative safety and efficacy of extended-release opioids for managing cancer pain concluded that one cannot confirm or rule out differences among the opioids due to a paucity of data from well-designed studies (11). Thus, it is important to determine whether individual opioids might have varying potentials for causing harm, particularly when combined with alcohol or drugs with central nervous system or respiratory depressant effects.

The objective of this study was to determine and quantify, using linear regression models, the relationship between various cointoxicants and decedent characteristics such as age and sex on the opioid concentrations identified in single opioid-induced deaths.

METHODS

Study Population

Drug-related deaths from West Virginia and the northern New England states of Maine, Vermont, and New Hampshire were analyzed. A forensic drug database (FDD) was initially created in 2005 to compile data from all drug-related deaths in West Virginia (WV). Data from 2007–2011 from the northern New England states of Maine (ME), Vermont (VT), and New Hampshire (NH) were later added to the WV data.

Each case in the FDD includes demographic information about the decedent (age, sex, zip code location of death), condition of the body, body mass index (BMI), cause and manner of death, contributory factors to death, all drugs identified as a direct cause or contributor to the death, the known or suspected route of drug administration, whether the decedent had a prescription for any controlled substances identified (available during this study period only for WV from the Controlled Substance Automated Prescription Program [CSAPP] database), medical history (for most decedents), key autopsy findings, and toxicological analyses (for each drug implicated in the death).

All four states in the study are served by centralized state medical examiner systems that perform comprehensive screening and quantification toxicology testing in all suspected drug deaths. All states maintain comprehensive digital and/or paper files, and each has statutes in place that require investigation and certification of all deaths suspected to be the result of, or that are associated with, drug intoxication. Although not an explicit policy during the study period, in all four states the usual practice of certification was to include potential cointoxicants on the death certificate.

Suspected drug deaths are investigated in a similar manner among the states, including examination of the body by a medical examiner or a certified death investigator who obtains peripheral blood samples and possibly additional body fluids for toxicological analysis. Data summarizing all medications belonging to the decedent, including unlabeled drugs, are submitted to the respective state’s Office of the Chief Medical Examiner (OCME). During the study period, all deaths resulting from drug intoxication received an autopsy in WV; the majority of such cases were autopsied in the northern New England states.

All four states are largely rural, with large areas of low population density, and have populations that are under two million and are overwhelmingly white. During the study period, both Maine and West Virginia had functioning prescription drug monitoring programs.

Study Sample

All drug-related deaths in the FDD from 2007–2011, defined as those deaths for which the medical examiner determined that at least one drug was a direct cause of death or a contributor to death, and the manner of death was ruled accidental, were included. The specific FDD subpopulation used for this study included accidental deaths involving any one of four opioids (oxycodone, methadone, hydrocodone, or fentanyl), along with at least one or more of the following selected cointoxicants: alcohol, alprazolam, diazepam, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitor antidepressants (SSRIs), and diphenhydramine (DPH). Eliminating all cases in which the body was noticeably decomposed further restricted the study sample.

Single opioid deaths involving oxycodone, methadone, hydrocodone, and fentanyl were selected because these opioids occurred most frequently in drug-related deaths in all four states. Multiple opioid deaths were removed for this study to reduce the potential for confounding during the analyses of potential cointoxicant associations, although these types of deaths are frequent enough to warrant additional future research. Of unintentional, nondecomposed cases with at least one of the four opioids named above, there were 744 deaths with two opioids mentioned on the death certificate, 141 deaths with three opioids, and nine deaths with four or more opioids. The most common multiple-opioid combination causing death involved hydrocodone and oxycodone, with 132 cases.

Variation among states, and between northern New England (NNE) and West Virginia, were initially examined to determine whether data from all the states could be combined. Neither the states nor the regions differed significantly with regard to median age, sex, BMI, or the prevalence of deaths involving TCAs, SSRIs, or alcohol. Nor did states differ when selecting decedents for toxicology analyses; all suspected drug-induced deaths received full toxicology testing. Because of these similarities, samples were combined for the purpose of examining cointoxication patterns. Our regression models do, however, adjust for the region of data collection, since the overall prevalence of opioid deaths was substantially higher in West Virginia than in Northern New England.

Toxicological Analyses

All involved states routinely screen blood or urine samples from each case for a panel of abused drugs using enzyme immunoassay, with confirmation analyses conducted based upon the substance(s) identified. Toxicological analyses of different body fluids/tissues are used as appropriate to confirm drug involvement in the deaths. Important metabolites of drugs identified are also measured and reported to further clarify the roles of specific drugs in the deaths as well as chronicity of use. Opioids and cointoxicants were detected in blood or urine by gas chromatography mass spectrometry (GC/MS), liquid chromatography-tandem mass spectrometry (LC/MS/MS) or liquid chromatography time-of-flight mass spectrometry

(LC/TOF-MS) screening. The analyses in this study were limited to subclavian or femoral blood samples, which are routinely used for toxicological analyses in each included state.

Statistical Analyses

Regression models were selected to examine the relationships between the opioid concentrations in the study cases and the following cointoxicants identified during toxicological analysis: benzodiazepines (specifically, alprazolam and diazepam, the most common benzodiazepine cointoxicants), alcohol, TCAs, SSRIs, and diphenhydramine. Additional covariates of state, age, BMI, and sex were included. Multiple regression is an extension of basic correlation to multiple dimensions and allows us to examine the associations after accounting for the other variables in the model. This method permits examination of multiple variables at once in order to explore relationships among them; it does not establish causation.

Due to the skewed nature of the opioid concentrations, log-opioid concentrations were modeled to satisfy the assumptions of linear regression. For each of the four opioids of interest, individual associations between log-opioid concentrations and each factor (sex, age, BMI, alprazolam presence, diazepam presence, alcohol level, TCA presence, SSRI presence, and diphenhydramine presence) were assessed using unadjusted linear regression. Additionally, a multiple linear regression was applied for each opioid to examine associations between each of these factors adjusting for the remaining factors. All regression models accounted for the state of data collection (NNE [ME, NH, VT] and WV).

Descriptive and empirical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). Findings were considered statistically significant for $p < 0.05$.

RESULTS

A total of 4702 drug-induced deaths were recorded in the FDD during the study period. The manner of death in most cases was certified as accidental (3884 cases) with the remainder undetermined (359 cases) or suicide (445 cases). Of the accidental drug-induced deaths, 1624 cases involved one or more pharmaceutical opioids specified on the death certificate as a cause or contributing factor in the death, along with at least one benzodiazepine (limited to diazepam or alprazolam), one antidepressant, alcohol, and/or diphenhydramine. As noted previously, we eliminated all cases observed to be decomposed. Of 1482 single opioid-cointoxicant deaths, 477 (32.2%) were from northern New England and 1005 (67.8%) were from West Virginia. The opioids present in this sample were: oxycodone (n=482), methadone (n=630), hydrocodone (n=183), and fentanyl (n=187). Cointoxicant alprazolam was present in 341 deaths, diazepam in 265 deaths, alcohol in 257 deaths, TCAs in 72 deaths, SSRIs in 104 deaths, and diphenhydramine in 71 deaths. Alcohol was further stratified according to whether the concentration was below or above the legal limit for driving intoxication of 0.08% utilized in the United States.

Table 1 summarizes the characteristics for each opioid subsample in the study. Although the NNE and WV regional populations differed significantly in terms of the prevalence of opioid, benzodiazepine, and alcohol involvement, they were not significantly different in

median age, sex ratio, and median BMI, as well as involvement of TCAs, SSRIs, and diphenhydramine. Thus, regions were combined to build the cointoxication model described below.

For the regression models, some records with missing factors (e.g., BMI) were excluded, as well as a small number of extreme opioid concentration measures (i.e., fentanyl 9.4 μg/mL; hydrocodone 32 μg/mL, 49 μg/mL, 190 μg/mL, and 1000 μg/mL; oxycodone 17 μg/mL and 50 μg/mL) that might have reflected erroneous data entry. Table 2 reports the estimated model effects of the factors analyzed upon log-opioid concentrations in log-μg/mL. The average differences from the adjusted models in Table 2 are presented in Table 3 using the more familiar μg/mL and showing the average magnitude and directionality of the association with opioid concentrations. Potentiation was not observed for benzodiazepine and alcohol alone for the concentrations of any of the four opioids studied, but the magnitude of the associations shown in the tables are additive. Somewhat unexpectedly, the patterns of significant association differed among the four opioids.

Utilizing the findings in both Table 2 (significance of the association for the study factors, focusing on the values adjusted for all other factors) and Table 3 (average model effect on opioid concentration in μg/mL), increasing age was the only non-drug factor significantly associated with decreased fentanyl concentrations (p=0.0218). The presence of a cointoxicant TCA was significantly related to lower fentanyl concentrations (p=0.0008) in the model, with an average 0.0075 μg/mL lower fentanyl concentration. None of the other cointoxicants in our model had a significant association with fentanyl concentrations.

Decreasing hydrocodone concentrations were significantly (p=0.0489) associated with increasing age, as well as the presence of several cointoxicants. Alprazolam presence was significantly (p=0.0064) associated with an average reduction in hydrocodone concentration by 0.0215 μg/mL in this model. Alcohol presence at or above 0.08% was significantly (p=0.0033) associated with a lower concentration of hydrocodone averaging 0.1641 μg/mL; alcohol presence below the legal level was associated with lower hydrocodone levels averaging 0.1164 μg/mL. Diphenhydramine presence was significantly (p=0.0437) associated with a lower average hydrocodone concentration of 0.0276 μg/mL. Male sex was significantly (p=0.0030) associated with a 0.0531 μg/mL lower methadone concentration on average. Any alcohol presence was significantly (p<0.0001) associated with lower methadone concentrations, ranging from approximately 0.12 μg/mL 0.1641 μg/mL on average. Neither alprazolam nor diazepam presence had a significant model effect on the average methadone concentration, nor did age or BMI.

The average oxycodone concentration was significantly (p=0.0066) associated with a lower cointoxicant alcohol concentration, ranging from an average of 0.0846 μg/mL when alcohol was less than 0.08% and 0.0482 μg/mL when alcohol was ≥ 0.08%. TCA presence was significantly (p=0.0012) associated with an average 0.0974 μg/mL lower oxycodone concentration.

DISCUSSION

Forensic pathologists face a daunting task in certifying overdoses as a cause of death, particularly when addressing complications of preexisting comorbidities and development of tolerance. Although it has been general practice of giving greater consideration to the probability of drug-associated deaths when multiple, potentially synergistic drugs are present, no systematic inquiry into the magnitude of this phenomenon on a drug by drug basis has been previously reported using large numbers of data as compiled by this study.

When opioids are present with cointoxicants, particularly other central nervous system and respiratory depressant drugs or alcohol, toxicity can be enhanced (12, 13). As a result, the opioid concentration found in decedents might be anticipated to be lower than expected and often in a nontoxic range (13–16). Minett et al. studied the association between high and low concentrations of psychoactive cointoxicants present in morphine-related deaths but did not find a significant relationship between high and low concentrations of cointoxicant benzodiazepines and alcohol and morphine concentrations (1). Interestingly, they found a significant positive association between morphine and antidepressant concentrations, with higher morphine concentrations associated with higher antidepressant concentrations. This finding is contrary to what would be expected with a synergistic central nervous system effect. Based on animal studies, the authors speculated it might have resulted from a chronic antidepressant inhibitory action on opioid effects, perhaps resulting from a decrease in opioid receptors in the cerebral cortex. However, the explanation for their finding is unknown and the study was limited by small numbers of cases.

Our study is unique in determining and quantitating the association of various cointoxicants and other decedent characteristics while adjusting for the presence of the other factors. Several interesting findings in our study merit discussion. First, significant associations were found between lower opioid concentrations and the presence of various cointoxicants, although considerable variability was found for fentanyl, hydrocodone, methadone, and oxycodone. Fentanyl and oxycodone concentrations were both found to be significantly lower with cointoxicant TCAs, but not the concentrations of the other two opioids. Methadone was the only opioid whose average concentration was significantly associated with the decedent’s sex. Increasing age was significantly associated with increases, not decreases, in fentanyl, hydrocodone, and methadone concentrations, but not in oxycodone concentrations. Alprazolam presence was only associated with a significant lowering of the average hydrocodone concentration, while no significant association was found between diazepam and concentrations of any of the four opioids. The presence of alcohol was significantly associated with lower concentrations of hydrocodone, methadone, and oxycodone, but not fentanyl.

Second, only hydrocodone levels were significantly associated with the presence of diphenhydramine, with a lower level comparable to the alcohol and alprazolam association. However, small sample sizes for diphenhydramine in the other opioid subsets, particularly for oxycodone, might have resulted in insufficient power for detecting significant associations. The potential additive effects of diphenhydramine as a cointoxicant in opioid-related deaths should be further studied.

Third, fentanyl was found to be rather unique in this study. This powerful opioid appeared to have been influenced to a lesser extent by cointoxicants in the fatalities, except, somewhat surprisingly, when tricyclic antidepressants were present. However, there were only eight cases with fentanyl and a cointoxicant TCA. More research on fentanyl and its relationships to other cointoxicants is needed, but the possibility for interactions with TCAs points to the importance of listing all potentially interacting drugs on the death certificate.

Alcohol was significantly associated with lower opioid concentrations for hydrocodone, methadone, and oxycodone, regardless of whether the alcohol concentration was above or below 0.08%. The effect of alcohol in the model was relatively strong for methadone and oxycodone. Interestingly, the alcohol association with oxycodone concentrations was greater for concentrations < 0.08% compared to higher alcohol concentrations. Since a fairly small subset of oxycodone decedents had the lower alcohol concentrations, they might not have reflected that actual population. Previous studies have reported that alcohol concentrations significantly decreased as the number of cointoxicants increased (13), and the presence of alcohol has been associated with lower concentrations of opioids such as methadone and heroin compared to those opioids alone (13, 17, 18). Thus, the potential cointoxicant effect of alcohol when present in opioid-related deaths should not be underestimated.

However, it was somewhat surprising that the quantitative association of alcohol with methadone and oxycodone concentrations was substantially greater than the association of benzodiazepines with the concentrations of those opioids. Diazepam presence was not associated with statistically significant differences in any of the opioid concentrations in this study, and alprazolam presence was only associated with a lower hydrocodone concentration. This latter finding might be at least partly explained by the fact that about 62% of hydrocodone deaths involved a benzodiazepine, predominantly alprazolam, which was a higher percentage than for the other three opioids.

The associations of the various factors and cointoxicants with opioid concentrations were found to be additive in this study. As a result, even though some of the individual associations appear to be fairly small, their possible additive contributions in opioid-related deaths could be substantial. For example, a previous analysis of DPH deaths found that over half of the DPH-related fatalities involved four or more drugs, with antidepressants often found as cointoxicants (8). Thus, in a hydrocodone-related death with a concentration of 0.08 μg/mL found on toxicological analysis, if DPH, a TCA, and alprazolam were also found to be cointoxicants, the additive effects of those cointoxicants in our model (−0.028 + −0.016 + −0.022), respectively, on the hydrocodone concentration might be comparable to an actual hydrocodone concentration of 0.146 μg/mL, almost double the concentration actually found.

One limitation of the current study is that it did not examine the potential contribution of underlying comorbid diseases such as heart disease or respiratory conditions (e.g., sleep apnea) on the concentration relationships reported. Methadone fatalities were reported to be significantly more likely to have underlying systemic diseases, particularly heart disease, compared to heroin users (18), and sleep apnea might be a predisposing factor to opioid toxicity (6). In addition, although efforts were made to ensure that data entry from the

medical examiners' files was accurate, this study was retrospective and errors in data extraction and entry are possible. Although this study included 1482 decedents, stratification by opioid and by cointoxicant substantially reduced the size of the subgroups, weakening the model. More research is needed to refine and test the associations found in our model. Large samples will be required to examine more complex polydrug cases, such as those involving more than one opioid with multiple cointoxicants.

CONCLUSION

The potential for additive effects of cointoxicant drugs and alcohol in opioid-related deaths should be considered when interpreting their roles in causing or contributing to those deaths. The presence of alcohol, benzodiazepines, and antidepressants was associated with significantly lower opioid concentrations, which may obscure the interpretation of postmortem toxicology results alone. The findings from the models used in this study can assist with such interpretations, especially in opioid deaths due to fentanyl, hydrocodone, methadone or oxycodone.

Opioids should not be treated as a homogenous group since specific opioids could vary in how they interact with cointoxicants. In particular, associations between fentanyl and TCAs and between hydrocodone and DPH require more research attention. This study underscores the importance of documenting all potential cointoxicants in single opioid-related deaths when entering cause of death on the death certificate. Future research efforts need to address the potential relationships among cointoxicants when multiple opioids are present.

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References

1. Minett WJ, Moore TL, Juhascik NP, et al. Concentrations of opiates and psychotropic agents in polydrug overdoses: a surprising correlation between morphine and antidepressants. J Forensic Sci. 2010 Sep; 55(5):1319–25. http://dx.doi.org/10.1111/j.1556-4029.2010.01408.x. [PubMed: 20456586]
2. Dasgupta N, Funk MJ, Proescholdbell S, et al. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. Pain Med. 2016 Jan; 17(1):85–98. http://dx.doi.org/10.1111/pme.12907. [PubMed: 26333030]
3. Davis GG. National Association of Medical Examiners and American College of Medical Toxicology Expert Panel on Evaluating and Reporting Opioid Deaths. National Association of Medical Examiners position paper: recommendations for the investigation, diagnosis, and certification of deaths related to opioid drugs. Acad Forensic Pathol. 2013 Mar; 3(1):77–83.
4. Warner M, Paulozzi LJ, Nolte KB, et al. State variation in certifying manner of death and drugs involved in drug intoxication deaths. Acad Forensic Pathol. 2013 Jun; 3(2):231–7.
5. Jones CM, Paulozzi LJ, Mack KA. Centers for Disease Control and Prevention (CDC). Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department

visits and drug-related deaths – United States, 2010. MMWR Morb Mortal Wkly Rep. 2014 Oct 10; 63(40):881–5. [PubMed: 25299603]

6. Webster LR, Cochella S, Dasgupta N, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. Pain Med. 2011 Jun; 12(Suppl 2):S26–35. http://dx.doi.org/10.1111/j.1526-4637.2011.01134.x. [PubMed: 21668754]
7. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. JAMA. 2013 Feb 20; 309(7):657–9. http://dx.doi.org/10.1001/jama.2013.272. [PubMed: 23423407]
8. Varghese EM, Abate MA, Hu L, et al. Characterization of diphenhydramine-related accidental overdose deaths. Acad Forensic Pathol. 2015 Mar; 5(1):105–115.
9. Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of opioids for nonmalignant pain in older adults. Arch Intern Med. 2010 Dec 13; 170(22):1979–86. http://dx.doi.org/10.1001/archinternmed.2010.450. [PubMed: 21149754]
10. Khodneva, Y., Muntner, P., Kertesz, S., et al. Prescription opioid use and risk of coronary heart disease, stroke, and cardiovascular death among adults from prospective cohort (REGARDS study). Pain Med. 2015 Sep 11. [Epub ahead of print]http://dx.doi.org/10.1111/pme.12916
11. Mesgarpour B, Griebler U, Glechner A, et al. Extended release opioids in the management of cancer pain: a systematic review of efficacy and safety. Eur J Pain. 2014 May; 18(5):605–16. http://dx.doi.org/10.1002/j.1532-2149.2013.00401.x. [PubMed: 24115561]
12. Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opioid and benzodiazepine combination use. Drug Alcohol Depend. 2012 Sep 1; 125(1–2):8–18. http://dx.doi.org/10.1016/j.drugalcdep.2012.07.004. [PubMed: 22857878]
13. Jones AW, Kugelberg FC, Holmgren A, Ahlner J. Drug poisoning deaths in Sweden show a predominance of ethanol in mono-intoxications, adverse drug-alcohol interactions and poly-drug use. Forensic Sci Int. 2011 Mar 20; 206(1–3):43–51. http://dx.doi.org/10.1016/j.forsciint.2010.06.015. [PubMed: 20630671]
14. Koski A, Vuori E, Ojanpera I. Relation of postmortem blood alcohol and drug concentrations in fatal poisonings involving amitriptyline, propoxyphene and promazine. Hum Exp Toxicol. 2005 Aug; 24(8):389–96. http://dx.doi.org/10.1191/0960327105ht542oa. [PubMed: 16138729]
15. Häkkinen M, Launiainen T, Vuori E, Ojanperä I. Comparison of fatal poisonings by prescription opioids. Forensic Sci Int. 2012 Oct 10; 222(1–3):327–31. http://dx.doi.org/10.1016/j.forsciint.2012.07.011. [PubMed: 22884575]
16. Pirnay S, Borron SW, Giudicelli CP, et al. A critical review of the causes of death among post-mortem toxicological investigations: analysis of 34 buprenorphine-associated and 35 methadone-associated deaths. Addiction. 2004 Aug; 99(8):978–88. http://dx.doi.org/10.1111/j.1360-0443.2004.00790.x. [PubMed: 15265095]
17. Paulozzi LJ, Logan JE, Hall AJ, et al. A comparison of drug overdose deaths involving methadone and other opioid analgesics in West Virginia. Addiction. 2009 Sep; 104(9):1541–8. http://dx.doi.org/10.1111/j.1360-0443.2009.02650.x. [PubMed: 19686524]
18. Darke S, Duflou J, Torok M. The comparative toxicology and major organ pathology of fatal methadone and heroin toxicity cases. Drug Alcohol Depend. 2010 Jan 1; 106(1):1–6. http://dx.doi.org/10.1016/j.drugalcdep.2009.07.014. [PubMed: 19720472]

Table 1

Cointoxication Factors and Subsample Sizes By Key Opiates

	Fentanyl	Hydrocodone	Methadone	Oxycodone	*p*-value
Categorical Factors*	**n (Column %)**	**n (Column %)**	**n (Column %)**	**n (Column %)**	
Region					< 0.0001
Northern New England 3 270 572 (64%)	44 (23.5)	20 (10.9)	270 (42.9)	143 (29.7)	
West Virginia 1 852 994 (36%)	143 (76.5)	163 (89.1)	360 (57.1)	339 (70.3)	
Total 5 123 566 (100%)	187 (12.6)	183 (12.4)	630 (42.5)	482 (32.5)	
Male	120 (64.2)	115 (62.8)	440 (69.8)	329 (68.3)	0.2185
Alprazolam Present	24 (12.8)	72 (39.3)	90 (14.3)	155 (32.2)	< 0.0001
Diazepam Present	36 (19.3)	41 (22.4)	102 (16.2)	86 (17.8)	0.2598
Alcohol Concentration†					0.0010
Absent	156 (83.4)	142 (77.6)	547 (86.8)	380 (78.8)	
< 0.08%	14 (7.5)	5 (2.7)	19 (3.7)	26 (5.4)	
≥0.08%	17 (9.1)	36 (19.7)	64 (10.2)	76 (15.8)	
TCA Present	8 (4.3)	8 (4.4)	24 (3.8)	32 (6.6)	0.1692
SSRI Present	16 (8.6)	14 (7.7)	42 (6.7)	32 (6.6)	0.7975
Diphenhydramine Present	9 (4.8)	14 (7.7)	31 (4.9)	17 (3.5)	0.1724
Continuous Factors‡	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
Age	40 (31, 48)	45 (36, 52)	36 (27, 46)	41 (33, 48)	<0.0001
BMI§	28.5 (24.8, 33.4)	29.2 (25.4, 36.1)	27.5 (23.7, 32.3)	28.0 (24.5, 33.4)	0.0072

*Pearson chi-square tests

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[†] Mantel-Haenszel tests, incorporating the ordered nature of alcohol level categories

[‡] Kruskal-Wallis nonparametric tests

[§] Some decedents were missing a valid height or weight; BMI could be calculated for the following cases: fentanyl (N = 182), hydrocodone (N = 178), methadone (N = 614), oxycodone (N = 470)

TCA = tricyclic antidepressant, SSRI = selective serotonin receptor inhibitor, BMI = body mass index, IQR = interquartile range

Table 2

Estimated Factor Effects (Unadjusted and Adjusted) on Log-Opioid Concentration (log-μg/mL)

	Fentanyl (n=181)		Hydrocodone (n=174)		Methadone (n=612)		Oxycodone (n=469)	
	Unadjusted*	Adjusted†	Unadjusted*	Adjusted†	Unadjusted*	Adjusted†	Unadjusted*	Adjusted†
Factor	**Standard Error**	**Standard Error**	**Standard Error**	**Standard Error**	**Standard Error**	**Standard Error**	**Standard Error**	**Standard Error**
Sex (Male)	**−0.349 (0.17) *p*=0.0450**	−0.220 (0.19)	0.013 (0.15)	0.130 (0.15)	**−0.258 (0.07) *p*<0.0001**	**−0.197 (0.07) *p*=0.0030**	0.010 (0.09)	−0.010 (0.09)
Age	0.014 (0.007)	**0.019 (0.01) *p*=0.0218**	0.011 (0.006)	**0.012 (0.1) *p*=0.0489**	**0.006 (0.003) *p*=0.0330**	**0.006 (0.002) *p*=0.0228**	−0.003 (0.004)	−0.003 (0.004)
BMI	−0.018 (0.01)	−0.016 (0.01)	0.002 (0.01)	0.004 (0.01)	−0.006 (0.004)	−0.006 (0.004)	−0.003 (0.005)	−0.002 (0.005)
Alprazolam	−0.106 (0.26)	−0.187 (0.26)	−0.200 (0.15)	**−0.460 (0.16) *p*=0.0064**	−0.046 (0.09)	−0.083 (0.09)	0.136 (0.09)	0.106 (0.10)
Diazepam	−0.232 (0.22)	−0.282 (0.22)	−0.132 (0.18)	−0.320 (0.19)	−0.117 (0.08)	−0.113 (0.08)	0.063 (0.11)	0.068 (0.12)
Alcohol	*p*=0.4056	*p*=0.3500	*p*=0.1031	***p*=0.0033**	***p*<0.0001**	***p*<0.0001**	***p*=0.0182**	***p*=0.0066**
<0.08% vs. Absent	−0.112 (0.32)	−0.109 (0.32)	−0.002 (0.44)	**0.004 (0.43)**	**−0.401 (0.17)**	**−0.376 (0.17)**	**−0.388 (0.19)**	**−0.485 (0.19)**
> 0.08% vs. Absent	−0.388 (0.29)	−0.469 (0.30)	−0.387 (0.18)	**−0.655 (0.19)**	**−0.619 (0.10)**	**−0.584 (0.10)**	**−0.247 (0.12)**	**−0.247 (0.12)**
TCA	**−1.137 (0.44) *p*=0.0099**	**−1.651 (0.48) *p*=0.0008**	−0.418 (0.35)	−0.339 (0.37)	−0.025 (0.16)	−0.141 (0.15)	**−0.526 (0.17) *p*=0.0017**	**−0.558 (0.17) *p*=0.0012**
SSRI	0.093 (0.30)	0.039 (0.30)	−0.120 (0.27)	−0.263 (0.28)	−0.051 (0.12)	0.004 (0.12)	−0.112 (0.17)	−0.069 (0.17)
DPH	0.266 (0.39)	0.048 (0.39)	**−0.556 (0.28) *p*=0.0473**	**−0.588 (0.29) *p*=0.0437**	0.074 (0.14)	−0.020 (0.14)	**−0.449 (0.23) *p*=0.0478**	−0.387 (0.23)

Concentration effects in bold are statistically significant

BMI = body mass index, TCA = tricyclic antidepressant, SSRI = selective serotonin receptor inhibitor, DPH = diphenhydramine

*Adjusted only for region of data collection

†Adjusted for sex, age, BMI, presence of alprazolam, presence of diazepam, alcohol level, presence of TCA, presence of an SSRI, presence of diphenhydramine and region of data collection

Table 3

Average Differences in Predicted Concentrations (μg/mL)

	Fentanyl	Hydrocodone	Methadone	Oxycodone
Male	−0.0009	0.0060	**−0.0531**	−0.0018
Alprazolam Present	−0.0008	**−0.0215**	−0.0225	0.0183
Diazepam Present	−0.0012	−0.0149	−0.0304	0.0117
Alcohol Concentration*				
< 0.08% vs. Absent	−0.0005	**0.0002**	**−0.1164**	**−0.0846**
≥ 0.08% vs. Absent	−0.0019	**−0.0276**	**−0.1641**	**−0.0482**
TCA Present	**−0.0075**	−0.0157	−0.0380	**−0.0974**
SSRI Present	0.0002	−0.0122	0.0011	−0.0120
Diphenhydramine Present	0.0002	−0.0276	−0.0053	−0.0672

Concentrations in bold are statistically significant

TCA = tricyclic antidepressants, SSRI = selective serotonin reuptake inhibitor antidepressants

*Statistical significance related to alcohol presence or absence; model analyses did not differentiate between lower and higher alcohol concentrations