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Cross-sectional cause of death comparisons for stimulant and opioid mortality in San Francisco, 2005–2015

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ABSTRACT

Background: Opioids and stimulants (e.g., cocaine or methamphetamine/amphetamine [MAMP]) are major contributors to acute substance toxicity deaths. Causes of stimulant death have received little attention. We sought to characterize and compare causes of death and significant contributing conditions among persons who died from acute opioid, cocaine, or MAMP toxicity.

Methods: We identified all opioid, cocaine, or MAMP deaths in San Francisco from 2005 to 2015 through the California Electronic Death Reporting System. Multivariable logistic regression analyses were used to estimate associations between acute substance toxicity deaths (opioid versus stimulant; cocaine versus MAMP), additional reported causes of death, and significant contributing conditions most often linked to opioid and stimulant use.

Results: From 2005–2015, there were 1252 opioid deaths and 749 stimulant deaths. Cocaine accounted for most stimulant deaths. Decedents with cardiac or cerebral hemorrhage deaths had higher adjusted odds of death due to acute stimulant toxicity versus acute opioid toxicity (aOR = 4.79, 95%CI = 2.88–7.96, $p < 0.01$; aOR = 58.58, 95%CI = 21.06–162.91, $p < 0.01$, respectively); no statistically significant associations were found for cocaine compared to MAMP deaths. Significant contributing cardiac conditions were associated with higher adjusted odds of stimulant compared to opioid (aOR = 1.46, 95%CI = 1.19–1.79, $p < 0.01$) and cocaine compared to MAMP death (aOR = 1.66, 95%CI = 1.13–2.45, p = .01).

Conclusions: Stimulant compared to opioid deaths tended to involve cardiac or cerebrovascular causes of death, and cocaine deaths were more likely than MAMP deaths to involve significant contributing cardiac conditions. Mounting evidence suggests that stimulant use be considered a cardio/cerebrovascular risk factor and clinical care be adjusted to address this heightened risk.

1. Introduction

Drug poisoning has been the leading cause of injury-related death in the United States every year since 2009 (Paulozzi et al., 2012) and mortality from all drugs has increased from 2002 to 2015 (National Institute on Drug Abuse, 2017; Rudd et al., 2016). Though opioids are a major driver of the rise in all-drug mortality (Rudd et al., 2016), stimulants (e.g., cocaine or methamphetamine/amphetamine [MAMP]) are major contributors to opioid-related mortality and may, in fact, contribute to even more deaths than opioids (Coffin et al., 2003). Since 2010, the number of cocaine deaths (without opioids) increased by nine percent in the United States (National Institute on Drug Abuse, 2017). There was also an increase in psychostimulant (including MAMP) deaths from 1999 to 2006, followed by a decline until 2008, and then an upward shift in death from 2008 to 2015 (Calcaterra and Binswanger, 2013; Hedegaard et al., 2017).

Research suggests demographic differences between opioid and stimulant deaths. First, in New York City from 1990 to 2000, cocaine deaths were more likely than opioid deaths to occur among older and Black or African American persons (Bernstein et al., 2007). A study of mortality among illicit drug users in the United States found differential hazard rate ratios for all-cause mortality for heroin-only versus cocaine-only users from 1991 to 2006 (Muhuri and Gfroerer, 2011). Cocaine and opioid deaths likely represent distinct groups, highlighting the need

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for targeted interventions by substance of use. To our knowledge, no demographic comparisons have been made comparing MAMP to other acute substance toxicity deaths.

The well-understood pathophysiology of opioid deaths (reduced respiratory effort (Dahan et al., 2010, 2013; Oderda et al., 2013)) and that suspected in stimulant deaths (cardiac and cerebrovascular conditions) may affect distinct populations. Cocaine use is strongly associated with electrophysiological and cellular cardiac toxicity (Stankowski et al., 2015), and MAMP is known to increase heart rate and blood pressure (Huang et al., 2016; Karch, 2009; Kaye et al., 2007), likely exerting physiologic and anatomic strain on the cardiovascular system. In a national study, stimulant deaths were most common among men between the ages of 45–54 and hypertension or other cardiac causes of death were also common (Calcaterra and Binswanger, 2013). Similarly, four studies of methamphetamine deaths found high prevalence of cardiovascular causes of death (Darke et al., 2017a,b; Herbeck et al., 2015; Darke et al., 2008). Another two studies found high risk of ischemic stroke and cerebral hemorrhage among methamphetamine users (Lappin et al., 2017; Ho et al., 2009), and yet another identified elevated risk of cerebrovascular conditions among both amphetamine and cocaine users (Westover et al., 2007).

Given these differences, and the limited literature comparing the population-level distribution and co-morbidities of opioid and stimulant deaths, we compared clinical conditions (i.e., cause of death and significant contributing conditions) of all opioid, cocaine, and MAMP deaths in San Francisco from 2005 to 2015. We specifically examined whether stimulant deaths were more likely than opioid deaths to involve cardiac and cerebrovascular causes of death and significant contributing conditions, and whether these differences persisted for cocaine compared to MAMP deaths.

2. Materials and methods

2.1. Opioid and stimulant death classification

Demographic data, substances involved in death, and clinical conditions (e.g., causes of death and significant contributing conditions) were abstracted from the California Electronic Death Reporting System (CA-EDRS) to create a database of all acute substance toxicity deaths occurring within the City and County of San Francisco between January 1, 2005 and December 31, 2015. The process by which acute substance toxicity deaths were classified was described in detail elsewhere (Visconti et al., 2015). Briefly, the San Francisco Office of the Chief Medical Examiner's (OCME) Forensic Laboratory Division performed toxicological screenings and confirmatory assessments of blood and urine specimens to identify substances that were causes of or significant contributors to death. For the purposes of this study, "acute substance toxicity deaths" comprised cases with causes of death listed as acute toxicity from substances (e.g., morphine, oxycodone, cocaine, methamphetamine, amphetamine, etc.). Cases that listed "acute [substance] toxicity," but did not specify which substances were involved underwent manual review by two physicians in consultation with the chief forensic toxicologist of the San Francisco OCME to determine substances involved. We selected cases based on review of causes of death for acute substance toxicity, rather than International Classification of Disease (ICD) codes, because the latter method has been shown to underestimate deaths where acute substance toxicity is involved (Ruhm, 2016). This study met the criteria for Human Subjects research exemption by the University of California, San Francisco Committee on Human Research (IRB #: 17-23209).

We restricted our analyses to decedents (i.e., cases who died) aged 18 and older with any acute opioid, cocaine, or MAMP toxicity listed as a cause of death and excluded cases that were non-accidental (i.e., due to homicide or suicide; Fig. 1). We defined "opioid deaths" as those with acute toxicity from prescription or non-prescription opioids (e.g., heroin, buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, propoxyphene, etc.) listed as a cause of death. "Stimulant deaths" were those with acute toxicity from cocaine or MAMP as a cause of death without opioids as a cause of death. Deaths involving both stimulants and opioids were classified as opioid deaths because opioids have a clear mechanism of death and we hypothesized (and evaluated in the present study) that deaths involving both stimulants and opioids would be more mechanistically similar to opioid deaths. "Cocaine deaths" and "MAMP deaths" were those with acute toxicity from cocaine or methamphetamine/amphetamine listed as a cause of death, respectively. Throughout the present analysis, we referred to "opioid deaths" interchangeably as deaths due to "acute opioid toxicity". This held for "stimulant deaths", "cocaine deaths", and "MAMP deaths."

2.2. Coding causes of death and significant contributing conditions

For the purposes of this study, "cause of death" was defined as the clinical condition(s) or events that directly lead to death according to the medical examiner determination. "Significant contributing conditions" were those that contributed to, but did not directly lead to death. Data abstracted from the CA-EDRS comprised multiple causes of death. For example, decedents with acute opioid toxicity listed as a cause of death could also have cerebral hemorrhage listed as a cause of death. For all deaths due to acute substance toxicity, we first enumerated all causes of death and significant contributing conditions. The study physician then categorized each result based on organ system or significant disease category (see Appendix Tables 1a, 1b, and 2 for the list of disease categories) and trained staff members in coding each case. To more concisely display descriptive results, causes of death and significant contributing conditions that could not be meaningfully grouped were categorized as "Other" (Tables 1 and 2). Though a large proportion of significant contributing conditions were categorized as "Other", quantitative findings were not influenced since we did not include the "Other" disease category in bivariable or multivariable analyses. Study staff consulted the study physician for a final decision when coding was unclear for any case. Once study staff completed the clinical coding, the study physician reviewed a random sample of 15% of decedents for quality control purposes. If less than a 95% coding match was reached between the study staff and physician, then the differences were reconciled by the study team and updates were applied to the rest of the dataset (i.e., if the same cause of death discrepancy was present in other cases that were not reviewed by the physician, then those cases were updated by study staff as well). Randomly-selected samples of 15% of the remaining cases were repeatedly sent to the study physician until over 95% match was reached.

Cardiac significant contributing conditions were ascribed to decedents with a cause of death or significant contributing condition listed as cardiac-related, since a medical examiner that coded a cause of death as due to a cardiac condition, such as coronary artery disease, generally did not also list that condition under significant contributing conditions.

2.3. Statistical analyses

Decedent race/ethnicity, sex, and age were included in bivariable analyses (chi-square test, *t*-test, or Fisher's exact test for small counts) to assess demographic differences for stimulant compared to opioid deaths and cocaine compared to MAMP deaths. We also adjusted for these variables in multivariable analyses given the disparities in acute substance toxicity deaths observed for these demographic groups (Rudd et al., 2016; Bernstein et al., 2007; Muhuri and Gfroerer, 2011). Race/ethnicity was coded according to Office of Management and Budget (OMB) standards (1997) and was collapsed further (Non-Hispanic/Latino[a] White, Black/African American, Asian/Pacific Islander, Other/Mixed, or Hispanic/Latino[a]) for bivariable and multivariable analyses