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Drug involvement in fatal overdoses

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ABSTRACT

Death certificate data from the Multiple Cause of Death (MCOD) files were analyzed to better understand the drug categories most responsible for the increase in fatal overdoses occurring between 1999 and 2014. Statistical adjustment methods were used to account for the understatement in reported drug involvement occurring because death certificates frequently do not specify which drugs were involved in the deaths. The frequency of combination drug use introduced additional uncertainty and so a distinction was made between *any* versus *exclusive* drug involvement. Many results were sensitive to the starting and ending years chosen for examination. Opioid analgesics played a major role in the increased drug deaths for analysis windows starting in 1999 but other drugs, particularly heroin, became more significant for recent time periods. Combination drug use was important for all time periods and needs to be accounted for when designing policies to slow or reverse the increase in overdose deaths.

1. Introduction

Fatal drug overdoses have reached epidemic levels in the United States, increasing 137% from 2000–2014 (Rudd, Aleshire, Zibbell, & Gladden, 2016). Growth in poisoning deaths, around 90% of which are now caused by drugs (Warner, Chen, Makuc, Anderson, & Miniño, 2011), were the most important source of the rise in the all-cause mortality rates of 45–54-year-old non-Hispanic whites occurring between 1999 and 2013 (Case & Deaton, 2015). The involvement of opioid analgesics (hereafter referred to as "opioids") and, more recently, heroin have received particular attention (Centers for Disease Control and Prevention, 2011, 2012; Jones, Logan, Gladden, & Bohm, 2015; Rudd et al., 2016; Volkow, Frieden, Hyde, & Cha, 2014), including a White House Summit in August 2014 (Hardesty, 2014).

Concerted efforts to lessen the severity of the opioid epidemic include establishing prescription drug monitoring programs, restricting the ability of pain clinics and online pharmacies to dispense oxycodone and other controlled substances, and developing abuse-deterrent formulations of some prescription drugs (Centers for Disease Control and Prevention, 2013; Finklea, Bagalman, & Sacco, 2013; Rannazzisi, 2013; Kirschner, Ginsburg, & Sulmasy, 2014). The federal Comprehensive Addiction and Recovery Act of 2016 (S. 524) supports expansions of drug diversion programs (reducing the criminality of low-level drug violations), medication assisted treatments, and the availability of naloxone administration for opioid overdoses.

However, there remain significant barriers to formulating effective policies to reverse or slow the rise in drug fatalities. One is that deadly overdoses frequently involve combinations of drugs in ways that are not fully understood (Jones, Mack, & Paulozzi, 2013; Paulozzi, Mack, & Hockenberry, 2014).[1] Second, we lack reliable knowledge of the specific drugs involved in poisoning fatalities because the drugs responsible are frequently left unspecified on death certificates. As a result, the contributions of specific drug categories or of drug combinations are understated.

Misunderstanding about these issues results in frequent erroneous statements being made about the nature of drug poisoning fatalities. In a typical example, Olsen (2016) states: "In 2014, nearly 20,000 deaths due to overdose of prescription opioids occurred in the United States". This is incorrect. An accurate characterization is that a prescription opioid was mentioned on the death certificates of around 20,000 fatalities classified as drug poisonings in that year. However, the actual number of cases involving opioids was certainly larger than this, because the drugs involved in these deaths were frequently not recorded. Conversely, prescription opioids may have *caused* either more or fewer fatalities because other drugs (particularly sedatives and psychotropic medications) were also implicated in many of these deaths. These issues become even more problematic when considering trends in fatal drug overdoses, since patterns of drug reporting and combination use have changed over time.

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[1] The term "overdoses" is used for convenience, while recognizing that some drug poisoning deaths are intentional.

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This analysis provides a first step in addressing several of these shortcomings and is innovative in three ways. First, statistical adjustment procedures recently developed by Ruhm (2016a) are extended and applied here to provide more accurate information on the drugs and drug combinations involved in fatal overdoses. These methods raise estimates of the involvement of specific drugs by 30% to >50% and emphasize the importance of drug "cocktails". Second, the adjusted estimates are used to examine which drug categories are responsible for the rapid rise in fatal overdoses. The frequency of multiple drug-taking introduces uncertainty, so a distinction is made between *any* versus *exclusive* drug involvement. Third, the investigation highlights the sensitivity of the findings to the choice of starting and ending years, revealing a key role of prescription opioids early in the data period but with other drugs, particularly heroin, and drug combinations being more important later.

2. Methods

2.1. Data

The primary outcomes are counts of drug poisoning deaths to US residents, using death certificate data from the 1999–2014 *Multiple Cause of Death* files (*MCOD*). The MCOD provide information on: a single underlying cause of death (UCD), up to twenty additional causes and some demographic data (Centers for Disease Control and Prevention, 2016). Cause-of-death was categorized using four-digit International Classification of Diseases, Tenth Revision (ICD-10) codes with details also provided on place of residence, age, race/ethnicity, sex, year, and weekday of death. The public use files lack geographic identifiers but restricted data on the state and county of residence were obtained for use in this study.

Poisoning deaths were defined using ICD-10 UCD codes, where the underlying cause is the "disease or injury that initiated the chain of morbid events that led directly and inevitably to death" (Centers for Disease Control and Prevention, 2014).[2] In cases of drug overdoses, the death certificate lists one or more drugs involved as immediate or contributory causes of death. These were included as ICD-10 "T-codes" and referred to here as drug involvement or mentions. The specific drug categories examined were: narcotics, sedatives, psychotropics, other specified drugs and unspecified drugs. Important subcategories were also analyzed. Narcotics were subdivided into opioid analgesics, heroin, cocaine and other narcotics, and psychotropics into antidepressants, antipsychotics and stimulants.[3] "Other specified" drugs included anesthetics, antiallergic and immunosuppressive drugs, histamine and anti-gastric secretion medications, cardiac drugs, antibiotics and many others. Poisoning by unspecified drugs, medicaments and biologicals (ICD-10 T-code, T50.9) is important because no specific drug was identified for 20–25% of fatal overdoses. Combination drug use was defined as the involvement of two or more of the drug categories: opioids, heroin, cocaine, other narcotics, sedatives, psychotropics or other drugs. This classification does not capture the use of multiple types of drugs within classes.[4]

The primary analysis began in 1999 because ICD-9 codes, used earlier, were not fully comparable to ICD-10 categories (Anderson, Miniño, Hoyert & Rosenberg, 2001). However, frequencies of drug poisoning deaths (but the not the specific drugs involved) could be compared using ICD-9 and ICD-10 codes, so public-use MCOD files for years before 1999 were used to conduct a descriptive investigation of broad trends in overdose fatalities from 1982–2014.

2.2. Analytic approach

The first step in determining which drug categories were responsible for the rise in overdose mortality involved accounting for fatalities where the death certificates did not specify the drugs involved. To do so, the analysis was limited to drug deaths and a dichotomous variable was constructed indicating if at least one drug type was mentioned on the death certificate, rather than only the unspecified category (ICD-10 T-code, T50.9). County-year averages of this variable were calculated and denoted as *SPECIFY*.

A series of probit models were next estimated to predict the determinants of specific drug mentions on death certificates. These models were run separately for each year and drug category (e.g. opioids in 2014) and also for drug combinations (more than one drug category reported). The specifications took the form:

$$Y_{ij} = \alpha + \beta SPECIFY_j + \gamma X_{ij} + \mu_{ij}, \quad (1)$$

where Y_{ij} was a binary dependent variable indicating if the overdose death for individual i in county j was reported to involve the specified drug (based on ICD-10 T-codes) or more than one category (i.e. a drug combination). Estimating separate models for each drug type and year allows the predicted effects of *SPECIFY*, and the other explanatory variables, to vary across drug classes and time periods. This could occur if, for example, some drug categories were reported more completely than others in areas with low rates of reporting, or if the reporting patterns changed over time.

In addition to *SPECIFY*, the models included supplementary covariates (X) for: sex, two race indicators (black, other nonwhite), currently married (versus never married, separated/divorced, widowed, or status not reported), four educational categories (less than high school graduate, high school graduate, some college, college graduate), eight age groups (≤20, 21–30, 31–40, 41–50, 51–60, 61–70, 71–80, >80), nine census regions (New England, Mid-Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain and Pacific) and seven day of the week indicators.[5] μ is an error term.

Predicted values of the dependent variables were calculated, for each drug poisoning death in the given year, and then averaged, to obtain mean predicted prevalences, $\overline{P}$:

$$\overline{P} = \frac{1}{n}\sum_{i=1}^{n}\Phi(\hat{Y}_{ij}) = \frac{1}{n}\sum_{i=1}^{n}\Phi\left(\hat{\alpha} + \hat{\beta} Specify_j + \hat{\gamma} X_{ij}\right), \quad (2)$$

for $\Phi(\boxdot)$ the cumulative distribution function of the standard normal distribution. Since these predictions were based on actual values of the explanatory variables, the estimated prevalences were expected to be close to the sample mean values. This was tested for and confirmed.

A second set of predicted values was obtained after setting *SPECIFY* to one for all drug deaths in the year. The average expected value, hereafter referred to as the "adjusted prevalence", $\widetilde{P}$, and estimated as:

$$\widetilde{P} = \frac{1}{n}\sum_{i=1}^{n}\Phi(\hat{\alpha} + \hat{\beta} + \hat{\gamma} X_{ij}), \quad (3)$$

indicates the involvement rate predicted for the specified drug category

[2] Poisoning deaths included ICD-10 UCD codes X40-X49, X60-X69, X85-X90 Y10-Y19, Y35.2, *U01(.6–.7); UCD codes for drug poisoning deaths were X40-X44, X60-X64, X85, Y10-Y14, Y35.2, *U01(.6–.7), (World Health Organization, 2014).

[3] Common opioid analgesics are oxycodone, methadone, hydrocodone and fentanyl. Antipsychotic medications include drugs such as: Thorazine (chlorpromazine), Compazine (prochlorperazine) and Haldol (haoperidol). Pschostimulants include methamphetamines, amphatamine salts (e.g. Adderall) and methylphenidates such as Ritalin and Concerta. Benzodiazepines, such as Valium (diazepam) and Xanax (alprazolam), are the most important subclass of sedatives, accounting for 84% of sedative-involved fatal overdoses in 2012 (Ruhm, 2016a).

[4] Psychotropics may be most important in this regard, since this category includes heterogeneous types of drugs. Warner, Trinidad, Bastian, Minino, and Hedegaard (2016) provide evidence that multiple types of opioids are frequently involved in fatal drug poisonings.

[5] Education was sometimes reported in years rather than specific thresholds. In these cases, ≤11, 12, 13–15 and ≥16 years were classified as less than high school graduate, high school graduate, some college and college graduate.