Drug and Alcohol Dependence 178 (2017) 501–511

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Increases from 2002 to 2015 in prescription opioid overdose deaths in combination with other substances

Denise B. Kandel[a,b,c,*], Mei-Chen Hu[a], Pamela Griesler[a,b], Melanie Wall[a,b,d]

[a] Department of Psychiatry, Columbia University, New York, NY 10032, USA
[b] New York State Psychiatric Institute, New York, NY 10032, USA
[c] Department of Sociomedical Sciences, Mailman School of Public Health, Columbia University, New York, NY 10032, USA
[d] Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY 10032, USA

ARTICLE INFO

Keywords:
Prescription opioids
Overdose deaths
Benzodiazepines
Heroin
Synthetic opioids other than methadone

ABSTRACT

Background: Prescription opioid (PO) overdose deaths increased sharply over the last decade. Changes in PO deaths in combination with other psychoactive substances may provide a partial explanation.

Methods: PO deaths from the National Multiple-Cause-of-Death Files for 2002–03 (N = 15,973) and 2014–15 (N = 41,491) were analyzed. We calculated (1) changes in proportions of deaths in combination with benzodiazepines, antidepressants, heroin, alcohol, cocaine between the two periods, and (2) proportions of increase in deaths attributable to each substance among PO and synthetic opioids other than methadone (SO-M) deaths, by age, gender, race/ethnicity.

Results: Between 2002–03 and 2014–15, PO deaths increased 2.6 times; SO-M deaths 5.6 times, especially for ages 18–34, males, African-Americans. For PO deaths, most frequent combinations at both periods were with benzodiazepines; for SO-M, benzodiazepines, antidepressants in 2002–03, heroin, benzodiazepines in 2014–15. The largest increases occurred in combination with heroin among all PO (4.6% to 15.4%, change ratio = 3.3[95%CI = 3.1–3.6]), but especially SO-M deaths (1.2% to 24.5%, change ratio = 21.3[95%CI = 15.0–30.3]). Deaths involving cocaine decreased among PO, increased among SO-M deaths. One-fifth of increased PO or SO-M deaths were attributable to any of the five substances. Increased PO deaths were equally attributable to benzodiazepines and heroin; deaths attributable to heroin were higher among ages 18–49, males, and non-Hispanic whites. Increased SO-M deaths were attributable mostly to heroin among all groups.

Conclusions: Increased PO overdose deaths over the last decade may be partially explained by increased deaths in combination with other psychoactive substances. Use of other substances should be considered in efforts toward reducing prescription opioid overdoses.

1. Introduction

Mortality and morbidity associated with prescription opioid analgesics increased sharply over the last decade (Centers for Disease Control and Prevention, 2017; Compton et al., 2015; Franklin et al., 2015; Kolata and Cohen, 2016; National Institute on Drug Abuse, 2017; Paulozzi, 2012; Rudd et al., 2016a; The White House, 2016; Volkow et al., 2014), leading the Centers for Disease Control to declare drug overdose deaths to be an epidemic (Rudd et al., 2016b). Prescription opioid (PO) overdose deaths increased more than two and a half times between 2002 and 2015 (National Institute on Drug Abuse, 2017). Increases in deaths occurred in the context of decreased prevalence of PO use but increased rates of heavy use and disorder among users (Han et al., 2015). Issues related to prescription opioids are worldwide, affecting European countries, Australia, and Canada (Berecki-Gisolf et al., 2017; Berterame et al., 2016; Degenhardt et al., 2013; Dhalla et al., 2011; European Monitoring Centre for Drugs and Addiction, 2014; Fischer et al., 2014; Shei et al., 2015; United Nations, 2006).

Determining the factors contributing to increased PO mortality is needed for informing prevention and intervention efforts. The director of the National Institute on Drug Abuse emphasized that increased prescriptions, greater social acceptability for using medications, and aggressive marketing by pharmaceutical companies helped create the "environmental availability" of prescription opioids and likely contributed to the current prescription drug abuse problem (Volkow, 2014). Increases in number of PO users could potentially explain

* Corresponding author at: Department of Psychiatry, Columbia University, 1051 Riverside Drive Unit 20, New York, NY 10032, USA.
E-mail address: dbk2@cumc.columbia.edu (D.B. Kandel).

http://dx.doi.org/10.1016/j.drugalcdep.2017.05.047
Received 13 April 2017; Received in revised form 26 May 2017; Accepted 27 May 2017
Available online 04 July 2017
0376-8716/

increases in PO deaths. Everything else constant, changes in number of deaths should parallel changes in number of users. However, a relationship between users and deaths cannot be directly established nationally. Records do not distinguish deaths related to medical or nonmedical prescription opioid (NMPO) use. Furthermore, trend data are only available for nonmedical PO use. Prevalence of NMPO use in the population declined (Frenk et al., 2015; Han et al., 2015) from 4.7% in 2002 to 3.9% in 2014 (Hu et al., 2017). The 8% increase in number of persons prescribed opioid analgesics from 75 million in 2002 to 81 million in 2014 (Hwang et al., 2016) paralleled the concurrent 10% increase in the US population size (288 million in 2002, 319 million in 2014). Consequently, the prevalence of individuals prescribed opioid analgesics remained flat, 26.0% in 2002, 25.4% in 2014. The evidence suggests that increased PO deaths did not result from an increased number of medical or nonmedical PO users.

Changes in PO users' behavior, including frequency of use, disorder, type of opioid used, prescription dosage, and concurrent use of other drugs, such as heroin or benzodiazepines, may account for increases in PO deaths (Compton et al., 2016; Drug Enforcement Administration, 2016; Hwang et al., 2016; Jones, 2012, 2013; Martins et al., 2017). High intensity NMPO use and disorder increased between 2002 and 2014 (Han et al., 2015; Hu et al., 2017; Jones, 2012). Prescription opioid dosage also increased since 1997 (Pain and Policy Studies Group/WHO Collaborating Center, 2015), and increased dosage is associated with increased morbidity and mortality (Bohnert et al., 2016; Dasgupta et al., 2016). Neither increasing intensity of use nor prescription dosage can be linked to population level PO overdose deaths because death records lack this information. Linkage can be implemented for one aspect of PO users' behavior prior to death, use of other drugs, since death records list contributing drugs. Use of PO in combination with other substances, e.g., benzodiazepines, alcohol, fentanyl-mixed heroin or cocaine, has been associated with increased mortality from additive or synergistic adverse effects in the US (Babalonis and Walsh, 2015; Centers for Disease Control and Prevention, 2016a; Jones et al., 2017; McCance-Katz et al., 2010; Oliver et al., 2007; Paone et al., 2016; Suzuki and El-Haddad, 2017), and Canada (Gomes et al., 2011), in part from pharmacokinetic and pharmacodynamic interactions resulting in respiratory depression and unintended rapid release of the opioid dose (Gudin et al., 2013; Jones et al., 2012; White and Irvine, 1999). Increased mortality associated with polydrug use involving opiates, cocaine, alcohol, or benzodiazepines in combination has been observed in New York City between 1990–98 (Coffin et al., 2003) and in Australia (Darke et al., 2010).

PO deaths involving other substances have been investigated at one time-point (Calcaterra et al., 2013; Dasgupta et al., 2016; Jann et al., 2014; Jones et al., 2013, 2014; Park et al., 2015; Saunders et al., 2012; Warner et al., 2016), but not over time, except for benzodiazepines (Chen et al., 2014; Jones and McAninch, 2015), which increased between 2004 and 2011 across age, gender and racial/ethnic groups (Jones and McAninch, 2015). Changes in overdose deaths from single substances, including heroin (Jones et al., 2015), psychostimulants (Calcaterra and Binswanger, 2013) and benzodiazepines (Bachhuber et al., 2016), have been examined separately up to 2009 or 2013. Using literal text analysis of information written on death certificates by medical certifiers (Trinidad et al., 2016; Warner et al., 2016), the National Center for Health Statistics and U.S. Food and Drug Administration recently identified specific drugs within classes of deaths in 2010–2014, and examined changes in all overdose deaths (not restricted to PO) for the ten most frequently mentioned specific drugs (Warner et al., 2016). Heroin deaths more than tripled; fentanyl deaths more than doubled.

The extent to which changes in PO deaths in combination with other substances contributed to the increase in PO deaths over the last decade and the relative contributions of different drug combinations to the increase remain to be specified.

We specify the extent to which changes in PO overdose deaths in combination with other substances contributed to increases in overall PO overdose deaths, and specifically synthetic opioids other than methadone (SO-M) overdose deaths which includes fentanyl, over the last twelve years in the population and in age, gender and race/ethnicity subgroups. We address three issues by analyzing national death records for 2002–03 and 2014–15 among all PO deaths, and among SO-M deaths, to capture indirectly changes related to fentanyl: (1) How has the proportion of PO deaths in combination with each of five central nervous system pharmaceutical or recreational psychoactive substances (benzodiazepines, antidepressants, heroin, alcohol, cocaine) changed in that interval? (2) What proportion of the increase in deaths is attributable to changes in deaths in combination with specific substances? (3) What are age, gender and racial/ethnic differences in these patterns?

2. Methods

2.1. Data

Data are from the Multiple-Cause-of-Death Files, National Vital Statistics System Wonder files (Centers for Disease Control and Prevention, 2016b) for PO overdose deaths for the years 2002–03 (N = 15,973) and 2014–15 (N = 41,491). One underlying cause-of-death, based on mechanism (e.g., overdose) and intent, and up to 20 contributing causes-of-deaths are recorded in death certificates (Slavova et al., 2015; Trinidad et al., 2016; Warner et al., 2016). Overdose/poisoning deaths involving PO are coded into three broad classes as per *International Classification of Diseases-Tenth Edition* (ICD-10) (National Center for Health Statistics, 2017): natural/semisynthetic opioids; methadone; synthetic opioids other than methadone (SO-M). Between 2002–2015, 17.0%–28.9% of drug overdose death certificates lacked information about contributing drugs (Rudd et al., 2016a; Trinidad et al., 2016; Warner et al., 2009, 2016).

The following ICD-10 codes were used for selecting cases:

(1) Drug overdose deaths: underlying cause of death X40–X44 (unintentional), X60–X64 (suicide), X85 (assault), Y10–Y14 (undetermined intent).
(2) PO overdose deaths: (1) and one contributing cause-of-death code T40.2 (natural and semisynthetic opioids, e.g., morphine, oxycodone, hydrocodone), T40.3 (methadone), T40.4 (SO-M, e.g., fentanyl, tramadol, propoxyphene, meperidine).
(3) SO-M overdose deaths: (1) and code T40.4 (SO-M).
(4) Heroin-related overdose: (1) and T40.1 (heroin).
(5) Benzodiazepine-related overdose: (1) and T42.4 (benzodiazepine).
(6) Antidepressant-related overdose: (1) and T43.0–T43.2 (antidepressant).
(7) Cocaine-related overdose: (1) and T40.5 (cocaine).
(8) Alcohol poisoning-related overdose: (1) and T51.0 (toxic ethanol effect), T51.9 (toxic effect of unspecified alcohol).

2.2. Variables

Gender: male, female.
Age: 0–17; 18–34; 35–49; 50 and older.
Race/ethnicity: non-Hispanic white; non-Hispanic African-American; Hispanic.

2.3. Analytical strategy

We examined changes in proportions of PO deaths in combination with other substances between 2002–03 and 2014–15 for all PO deaths and for SO-M deaths. We calculated (1) changes in proportions of deaths in combination with benzodiazepines, antidepressants, heroin, alcohol, or cocaine between 2002–03 and 2014–15, and (2) the proportion of increase in deaths attributable to each substance in combination, as the difference between actual and expected number of deaths