Quantifying the Epidemic of Prescription Opioid Overdose Deaths

In 2016, 63 632 persons died of a drug overdose in the United States; 66.4% (42 249) involved an opioid.[1] Opioid-involved deaths include prescription opioid analgesics (e.g., morphine, oxycodone), illicit opioids (e.g., heroin, illicitly manufactured fentanyl [IMF]), or both. Although prescription and illicit opioid overdoses are closely entwined,[2] it is important to differentiate the deaths to craft appropriate prevention and response efforts. Unfortunately, disentangling these deaths is challenging because multiple drugs are often involved. Additionally, death certificate data do not specify whether the drugs were pharmaceutically manufactured and prescribed by a health care provider, pharmaceutically manufactured but not prescribed to the person (i.e., diverted prescriptions), or illicitly manufactured.

THE CHANGING OPIOID OVERDOSE EPIDEMIC

The United States has seen rapid changes in the illicit opioid supply. Availability of illicitly manufactured synthetic opioids (e.g., fentanyl) that traditionally were prescription medications has increased. This has blurred the lines between prescription and illicit opioid-involved deaths. In one study in 27 states, Gladden et al.[3] examined data on drug products obtained by law enforcement that tested positive for fentanyl (fentanyl submissions) and deaths involving synthetic opioids other than methadone (referred to as synthetic opioids). From 2013 to 2014, fentanyl submissions increased by 426%. The increases were strongly correlated with increases in synthetic opioid deaths but not with pharmaceutical fentanyl prescribing rates, suggesting that the increases were largely due to IMF.[3] In a recent report, fentanyl was detected in at least half of the opioid overdose deaths from July to December 2016 in 7 of the 10 states examined.[4]

Traditionally, the Centers for Disease Control and Prevention (CDC) and others have included synthetic opioid deaths in estimates of "prescription" opioid deaths. However, with IMF likely being involved more recently, estimating prescription opioid–involved deaths with the inclusion of synthetic opioid–involved deaths could significantly inflate estimates.

MORE CONSERVATIVE ESTIMATION APPROACH

A new, more conservative estimation of prescription opioid–involved deaths is proposed to better differentiate deaths involving prescription (pharmaceutically manufactured) opioids from deaths involving illicit opioids (heroin, IMF). Pharmaceutically manufactured opioids are considered prescription opioids for estimation purposes because most persons misusing them reported obtaining them in a way that originated with a prescription (misusing own prescription or obtaining from friends or relatives). Only 4.9% bought opioids from a drug dealer or stranger, and 5.6% reported obtaining them by stealing from a doctor's office, clinic, hospital, or pharmacy or in some other way.[5]

The National Vital Statistics System (NVSS) multiple cause-of-death mortality files record drug overdose deaths, which are identified with the *International Classification of Diseases, 10th Revision* (*ICD-10;* Geneva, Switzerland: World Health Organization; 1992), according to the underlying cause-of-death codes X40 to X44 (unintentional), X60 to X64 (suicide), X85 (homicide), or Y10 to Y14 (undetermined intent). Among deaths with drug overdose as the underlying cause, the type of opioid is indicated by the following *ICD-10* multiple cause-of-death codes: opium (T40.0); heroin (T40.1); natural and semisynthetic opioids (T40.2); methadone (T40.3); synthetic opioids other than methadone (T40.4); and other and unspecified narcotics (T40.6).

Under the CDC's traditional method of calculating prescription opioid overdose deaths with NVSS, deaths involving natural and semisynthetic opioids and synthetic opioids as well as methadone are included. Under a more conservative method, deaths involving only natural and semisynthetic opioids and methadone are included. Deaths involving synthetic opioids are removed and calculated separately because of the high proportion of deaths that likely involve IMF.

With the traditional method, an estimated 32 445 prescription opioid–involved deaths occurred in 2016. With the more conservative method, 17 087 prescription opioid–involved deaths occurred in 2016 (Table 1). Longitudinal trends indicated a rapid increase in death rates involving synthetic opioids from 2013 to 2016 (annual percent change = 87.7%), whereas death rates involving natural and

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Note. *The findings and conclusions of this editorial are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.*

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TABLE 1—Prescription Opioid Overdose Deaths, Inclusive and Exclusive of Synthetic Opioids: United States, 1999–2016

	Conservative Definition for Prescription Opioids: Natural and Semisynthetic Opioids and Methadone[a]		Traditional Definition for Prescription Opioids: Natural and Semisynthetic Opioids, Methadone, and Other Synthetic Opioids[a]		Synthetic Opioids, Other Than Methadone[a]	
Year	No.	Overdose Deaths[b] per 100 000[c]	No.	Overdose Deaths[b] per 100 000[c]	No.	Overdose Deaths[b] per 100 000[c]
1999	3 442	1.2	4 030	1.4	730	0.3
2000	3 785	1.3	4 400	1.5	782	0.3
2001	4 770	1.7	5 528	1.9	957	0.3
2002	6 483	2.3	7 456	2.6	1 295	0.4
2003	7 461	2.6	8 517	2.9	1 400	0.5
2004	8 577	2.9	9 857	3.4	1 664	0.6
2005	9 612	3.2	10 928	3.7	1 742	0.6
2006	11 589	3.9	13 723	4.6	2 707	0.9
2007	12 796	4.2	14 408	4.8	2 213	0.7
2008	13 149	4.3	14 800	4.8	2 306	0.8
2009	13 523	4.4	15 597	5.0	2 946	1.0
2010	14 583	4.7	16 651	5.4	3 007	1.0
2011	15 140	4.9	16 917	5.4	2 666	0.8
2012	14 240	4.5	16 007	5.1	2 628	0.8
2013	14 145	4.4	16 235	5.1	3 105	1.0
2014	14 838	4.6	18 893	5.9	5 544	1.8
2015	15 281	4.7	22 598	7.0	9 580	3.1
2016	17 087	5.2	32 445	10.2	19 413	6.2

Note. Deaths are classified according to the *International Classification of Diseases, 10th Revision*. Drug overdose deaths are identified with underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. The following multiple cause-of-death codes were used to identify specific drug types: T40.2 for natural and semisynthetic opioid analgesics, T40.3 for methadone, and T40.4 for synthetic opioid analgesics other than methadone. Approximately one fifth of drug poisoning deaths lack information on the specific drugs involved. Additional information available at: https://www.cdc.gov/drugoverdose/data/analysis.html.

Source. Centers for Disease Control and Prevention. CDC WONDER: Mortality. Atlanta, GA: US Department of Health and Human Services; 2017. Available at: https://wonder.cdc.gov. Accessed December 22, 2017.

[a]Natural opioids include morphine and codeine, and semisynthetic opioids include drugs such as oxycodone, hydrocodone, hydromorphone, and oxymorphone. Methadone is a synthetic opioid. Synthetic opioids, other than methadone, include drugs such as tramadol and fentanyl.

[b]Deaths may involve one or more drugs.

[c]Age-adjusted rate, calculated with the direct method and the 2000 standard population.

semisynthetic opioids remained relatively stable from 2009 to 2016 (annual percent change = 3.4%).[1] Death rates involving methadone have significantly decreased since 2006 (annual percent change = 6.2%).[1] Thus, rates of prescription opioid–involved deaths estimated with the traditional method may have been inflated in recent years because of the increase in death rates involving synthetic opioids (e.g., fentanyl).

Limitations of the more conservative method include underestimating prescription opioid–involved deaths because it excludes prescription synthetic opioid deaths (e.g., fentanyl patch, tramadol). The number of prescription opioid–involved deaths that included diverted prescriptions or those that were counterfeit and imported illegally from other countries remains unknown. Toxicology testing cannot distinguish between pharmaceutical fentanyl and IMF[3]; therefore, all deaths involving synthetic opioids are removed in the conservative method and reported as their own category. Furthermore, drugs are not specified on the death certificate in approximately 20% of overdose deaths, which leads to an underestimation of opioid-involved deaths.[1] Finally, in 2014, multiple drugs were involved in almost half of the drug overdose deaths that mentioned at least one specific drug on the death certificate (36 667 deaths).[2] Therefore, opioids may not have been the only drug involved, or multiple opioids may have been involved.

CONCLUSIONS

Although the new approach is more conservative, this estimate may better represent prescription opioid–involved deaths because deaths likely involving IMF are excluded. Opioid-involved deaths were at their greatest levels ever in 2016. Prescription opioid–involved deaths estimated more conservatively have leveled off since 2012. However, the traditional measure has shown sharp increases from 2014 through 2016, paralleling increases in synthetic opioid deaths. Death rates under both measures remain alarmingly high.

Because of the increasing evidence that deaths involving synthetic opioids are likely a result of IMF, this more conservative approach likely provides a relatively more accurate number of prescription opioid–involved deaths, even though it excludes synthetic opioids that may have been pharmaceutically manufactured and prescribed. The traditional approach to NVSS analysis does not adequately reflect the changing landscape of the opioid overdose epidemic, which has become increasingly worse because of illicit opioids. Advances in surveillance, such as the CDC National Center for Injury Prevention and Control's State Unintentional Drug Overdose

Reporting System, which currently funds 32 states and Washington, DC, allow for data abstraction from preliminary death certificates and medical examiner or coroner reports on unintentional and undetermined opioid overdose deaths, with detailed data from death scene investigations and toxicology testing. With expanded surveillance improvements, CDC can disentangle prescription and illicit opioid-involved deaths more effectively, with specific drug types, such as IMF, identified.[4]

Obtaining an accurate count of the true burden and differentiating between prescription and illicit opioid-involved deaths are essential to implement and evaluate public health and public safety efforts. Distinct prevention strategies are required. In addition, if deaths involving synthetic opioids—likely IMF—are categorized as prescription opioid overdose deaths, then the ability to evaluate the effect of interventions targeting high-risk prescribing practices (e.g., guidelines, prescription drug monitoring programs) on prescription opioid–involved deaths is hindered. Decreases in prescription opioid–involved deaths could be masked by increases in IMF deaths, resulting in inaccurate conclusions.

Strategies to prevent prescription opioid misuse and overdose may include academic detailing on the CDC "Guideline for Prescribing Opioids for Chronic Pain"[6] and improving prescription drug monitoring program use. These interventions also could potentially reduce illicit opioid use and overdose long term. However, in areas experiencing an influx of IMF, increasing access to naloxone, educating emergency responders about higher dosage requirements, and enhancing law enforcement strategies to remove illicit drugs could have effects. Increasing linkages to risk reduction programs and medication-assisted treatment also is critical for persons with opioid use disorder.[7] Finally, enhanced toxicology testing, reporting of the specific drugs involved in deaths, and law enforcement strategies that target illicit drug diversion and availability are important complements. Ultimately, urgent work remains to end the opioid overdose epidemic. A collaborative approach between public health, clinical medicine, and law enforcement holds the greatest promise. AJPH

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