Letters

RESEARCH LETTER

Changes in Synthetic Opioid Involvement in Drug Overdose Deaths in the United States, 2010-2016

Drug overdose deaths are at unprecedented levels in the United States.[1] Prescription opioids have been the most common drug involved in overdose deaths, but heroin and synthetic opioids (primarily illicit fentanyl) are increasingly implicated in overdoses.[2] In addition, synthetic opioids are increasingly found in illicit drug supplies of heroin, cocaine, methamphetamine, and counterfeit pills.[3] To date, the involvement of synthetic opioids in overdose deaths involving other drugs is not well characterized, limiting the ability to implement effective clinical and public health strategies. Using 2010-2016 mortality data, we describe recent trends for synthetic opioid involvement in drug overdose deaths.

Methods | This research was exempt from institutional review board review by regulation. Data are from the National Vital Statistics System multiple cause of death file, based on death certificates submitted by medical examiners and coroners[1] and including information on all deaths in the United States. Drug overdose deaths were those assigned an underlying cause of death using the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes (X40-X44 [unintentional], X60-X64 [suicide], X85 [homicide], and Y10-Y14 [undetermined intent]). Among drug overdose deaths, opioid-related deaths were those assigned *ICD-10* codes T40.0 to T40.4, and T40.6. Prescription opioids were defined as natural/semi-synthetic opioids (T40.2) and methadone (T40.3); heroin (T40.1); synthetic opioids excluding methadone (T40.4); cocaine (T40.5); psychostimulants with abuse potential (T43.6); benzodiazepines (T42.4); antidepressants (T43.0-T43.2); antipsychotics and neuroleptics (T43.3-T43.5); barbiturates (T42.3); other illicit drugs (cannabis, lysergic acid diethylamide [LSD], and other hallucinogens, T40.7-T40.9); and alcohol (T51.0).

We calculated the number of synthetic opioid-involved overdose deaths by year for 2010 through 2016 overall and the number and percentage of overdose deaths involving the psychotherapeutic and illicit drugs listed above in which synthetic opioids were involved in the death. In addition, we calculated the number and percentage of synthetic opioid overdose deaths in 2016 also involving any drug or alcohol and psychotherapeutics, illicit drugs, or alcohol. The Joinpoint Regression Program (National Cancer Institute), version 4.3.1.0, was used to examine statistically significant changes in trends (eg, *P* trend) from 2010 through 2016. Because National Vital Statistics System data are not drawn from a sample but represent the full census of deaths in the United States, standard errors and CIs for estimates were not included. A 2-sided *P* value less than .05 was considered statistically significant.

Results | Among the 42 249 opioid-related overdose deaths in 2016, 19 413 involved synthetic opioids, 17 087 involved prescription opioids, and 15 469 involved heroin. Synthetic opioid involvement in these deaths increased significantly from 3007 (14.3% of opioid-related deaths) in 2010 to 19 413 (45.9%) in 2016 (*P* for trend <.01). Significant increases in synthetic opioid involvement in overdose deaths involving prescription opioids, heroin, and all other illicit or psychotherapeutic drugs were found from 2010 through 2016 (**Table**).

Among synthetic opioid–related overdose deaths in 2016, 79.7% involved another drug or alcohol. The most common coinvolved substances were another opioid (47.9%), heroin (29.8%), cocaine (21.6%), prescription opioids (20.9%), benzodiazepines (17.0%), alcohol (11.1%), psychostimulants (5.4%), and antidepressants (5.2%) (**Figure**).

Discussion | In 2016, synthetic opioids eclipsed prescription opioids as the most common drug involved in overdose deaths in the United States. These findings underscore the rapidly increasing involvement of synthetic opioids in the drug overdose epidemic and in recent increases in overdose deaths involving illicit and psychotherapeutic drugs. This analysis was limited by the 15% to 25% of death certificates in which the type of drug(s) involved in the overdose was not specified, an omission due to lack of toxicological testing or failure to record test results on death certificates. Thus, the numbers reported are likely underestimates. In addition, some of the increase in synthetic opioid involvement found in this study may be related to increased testing and detection of synthetic opioids.

Lack of awareness about synthetic opioid potency, variability, availability, and increasing adulteration of the illicit drug supply poses substantial risks to individual and public health.[4,5] Widespread public health messaging is needed, and clinicians, first responders, and lay persons likely to respond to an overdose should be trained on synthetic opioid risks and equipped with multiple doses of naloxone. These efforts should be part of a comprehensive strategy to reduce the illicit supply of opioids and expand access to medication-assisted treatment for opioid addiction.

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Concept and design: All authors.

Table. Synthetic Opioid Involvement in Overdose Deaths[a] Involving Illicit and Psychotherapeutic Drugs in the United States, 2010-2016

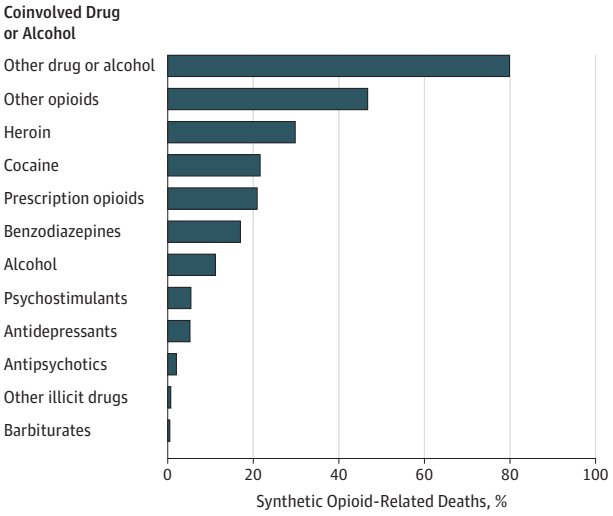
Drug Class	2010		2011		2012		2013		2014		2015		2016		*P* Value for Trend[b]
	Total Overdose Deaths, No.	Deaths Involving Synthetic Opioids, No. (%)	Total Overdose Deaths, No.	Deaths Involving Synthetic Opioids, No. (%)	Total Overdose Deaths, No.	Deaths Involving Synthetic Opioids, No. (%)	Total Overdose Deaths, No.	Deaths Involving Synthetic Opioids, No. (%)	Total Overdose Deaths, No.	Deaths Involving Synthetic Opioids, No. (%)	Total Overdose Deaths, No.	Deaths Involving Synthetic Opioids, No. (%)	Total Overdose Deaths, No.	Deaths Involving Synthetic Opioids, No. (%)	
Drug overdose deaths	38 329	3007 (7.8)	41 340	2666 (6.4)	41 502	2628 (6.3)	43 982	3105 (7.1)	47 055	5544 (11.8)	52 404	9580 (18.3)	63 632	19 413 (30.5)	<.01
Synthetic opioids[c]	3007	788 (26.2)	2666	729 (27.3)	2628	822 (31.3)	3105	746 (24.0)	5544	1358 (24.5)	9580	2248 (23.5)	19 413	4414 (22.7)	.03
Any opioid	21 089	3007 (14.3)	22 784	2666 (11.7)	23 166	2628 (11.3)	25 052	3105 (12.4)	28 647	5544 (19.4)	33 091	9580 (29.0)	42 249	19 413 (45.9)	<.01
Prescription opioids	14 583	939 (6.4)	15 140	889 (5.9)	14 240	861 (6.0)	14 145	1015 (7.2)	14 838	1489 (10.0)	15 281	2263 (14.8)	17 087	4055 (23.7)	<.01
Heroin	3036	45 (1.5)	4397	44 (1.0)	5925	69 (1.2)	8257	209 (2.5)	10 574	1027 (9.7)	12 989	2685 (20.7)	15 469	5781 (37.4)	<.01
Cocaine	4183	167 (4.0)	4681	189 (4.0)	4404	182 (4.1)	4944	245 (5.0)	5415	628 (11.6)	6784	1542 (22.7)	10 375	4184 (40.3)	<.01
Psychostimulants	1854	73 (3.9)	2266	93 (4.1)	2635	91 (3.5)	3627	142 (3.9)	4298	276 (6.4)	5716	494 (8.6)	7542	1042 (13.8)	<.01
Benzodiazepines	6497	746 (11.5)	6872	665 (9.7)	6524	655 (10.0)	6973	804 (11.5)	7945	1222 (15.4)	8791	1801 (20.5)	10 684	3308 (31.0)	<.01
Antidepressants	3889	568 (14.6)	4113	463 (11.3)	4259	464 (10.9)	4458	571 (12.8)	4768	723 (15.2)	4894	808 (16.5)	4812	1002 (20.8)	.04
Antipsychotics and neuroleptics	1351	184 (13.6)	1321	131 (9.9)	1333	144 (10.8)	1474	172 (11.7)	1588	224 (14.1)	1665	282 (16.9)	1877	385 (20.5)	.04
Barbiturates	296	33 (11.1)	315	28 (8.9)	323	34 (10.5)	335	38 (11.3)	320	33 (10.3)	404	56 (13.9)	409	88 (21.5)	.02
Other illicit drugs	190	17 (8.9)	229	18 (7.9)	243	17 (7.0)	274	22 (8.0)	300	41 (13.7)	427	68 (15.9)	543	144 (26.5)	<.01

[a] Deaths are not mutually exclusive. Deaths involving >1 drug or drug class are counted multiple times.

[b] Based on joinpoint regression analysis.

[c] For the synthetic opioids category, the columns for "deaths involving synthetic opioids" represent deaths in which synthetic opioids were the only drug involved in the overdose.

Figure. Percentage of Synthetic Opioid-Related Overdose Deaths Involving Illicit or Psychotherapeutic Drugs or Alcohol in the United States, 2016



[a] Deaths are not mutually exclusive. Percentages sum to more than 100%.

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Disclaimer: The findings and conclusions of this study are those of the authors and do not necessarily reflect the views of the Substance Abuse and Mental Health Services Administration or the National Institute on Drug Abuse of the National Institutes of Health.

1. Centers for Disease Control and Prevention. *National Vital Statistics System 2016 Multiple Cause of Death File*. Hyattsville, MD: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2017.

2. Rudd RA, Seth P, David F, Scholl L. Increases in drug and opioid-involved overdose deaths—United States, 2010-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(5051):1445-1452.

3. Drug Enforcement Administration. National drug threat assessment, 2017. https://www.dea.gov/docs/DIR-040-17_2017-NDTA.pdf. Accessed December 23, 2017.

4. Tomassoni AJ, Hawk KF, Jubanyik K, et al. Multiple fentanyl overdoses—New Haven, Connecticut, June 23, 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66(4):107-111.

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COMMENT & RESPONSE

Cervical Pessary and Spontaneous Preterm Birth

To the Editor Dr Saccone and colleagues[1] conducted a randomized clinical trial on the effect of a cervical pessary in women with singleton pregnancies and short cervical length and found that a pessary compared with no pessary resulted in a lower rate of spontaneous preterm birth. The authors achieved exactly their trial registry-planned sample size of 300, with 100% follow-up and 100% adherence to treatment allocation in both groups. The adherence seems implausible, as my patients commonly request removal for discomfort or other reasons.

In addition, exactly equal numbers of 150 women were randomized to each group. Women were "randomized by a web-based system ... implemented by use of a central telephone number." According to the protocol, http://www.randomization.com was used, and this can produce exactly 150 per group if 25 randomized blocks each of size 2, 4, and 6 are entered. But "randomization was stratified by cervical length (≤20 mm or >20 mm to ≤25 mm)," so separate random sequences must have been created for each stratum. For example, in the stratum with cervical length more than 20 mm (Table 1 in the article), 17 women (150 minus 133) were recruited in the pessary group and 25 (150 minus 125) in the control group. This imbalance of 8 is impossible with balanced blocks of 2, 4, and 6. At most, the imbalance would be 3, if recruitment ended halfway through a block of 6 with 3 same allocations in a row.

There is also a problem with the Kaplan-Meier analysis presented in the article's Figure 2A (all delivery types) and Figure 2B (spontaneous delivery only). The curves differ, albeit not by much, but the numbers at risk at each gestation were identical. Could one of the sets of numbers at risk be wrong?

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1. Saccone G, Maruotti GM, Giudicepietro A, Martinelli P; Italian Preterm Birth Prevention (IPP) Working Group. Effect of cervical pessary on spontaneous preterm birth in women with singleton pregnancies and short cervical length: a randomized clinical trial. *JAMA*. 2017;318(23):2317-2324.

In Reply As Dr Thornton suggests, one of the strengths of our trial was the 100% follow-up and the 100% adherence to the treatment allocation in the pessary group. These high rates were obtained because all women included in the trial delivered at the study institution. Moreover, included women were extensively informed by the research staff about the risk of preterm delivery. We strongly believe that all women would keep a cervical pessary if clinicians clearly explained to them that the benefits of having a healthy full-term infant outweigh the risk of having discomfort. Indeed, almost all women in the pessary group experienced some adverse effects (86.7% had vaginal discharge and 3.3% had pelvic discomfort) but none of them had the device removed. Effective physician-patient communication is a central clinical function in building a therapeutic relationship.[1]