

Letters

RESEARCH LETTER

Association of Medical Stimulants With Mortality in the US From 2010 to 2017

The role of nonopioids in the drug overdose epidemic in the US is frequently overshadowed. From 2015 to 2016, mortality rates involving cocaine and psychostimulants were smaller than opioids, but were rising faster than opioids.¹ We examined individual substances listed on death certificates to better understand stimulant-associated mortality and assess rates over time.

Methods | We used the Drug Involved Mortality database from the National Center for Health Statistics,² which comprised drug-related terms mentioned on death certificates for every death in the US from 2010 to 2017. All involved drugs from the death certificate part I, part II, and



Supplemental content

box 43 were used. Demographic characteristics as listed on the death certificate, polysubstance deaths, and mortality rates were analyzed for 3 subgroups: (1) all stimulants, (2) illicit stimulants (eg, cocaine), and (3) medical stimulants (eg, methylphenidate) (subgroups are defined in the eTable in the Supplement). If a death involved multiple drugs, it was counted in each of the drug groups; this resulted in double counting between rate estimates for individual drugs. Annual rate ratios (ARRs) were modeled using a Poisson mixed model regression. The Colorado Multiple institutional review board confirmed this analysis of deidentified decedent data to be not human participants research, and it was considered exempt from informed consent. Statistical analysis was conducted by the Researched Abuse, Diversion and Addiction-Related Surveillance System using SAS,

version 9.4 (SAS Institute), and statistical analysis was set at $P < .05$.

Results | Of the 1 220 143 deaths with involved drugs listed on the death certificate, 130 560 (10.7% of all decedents) were found to have stimulants listed. Among stimulant-involved deaths, 93 689 decedents (71.8%) were men, the median (interquartile range) age was 45 (34-54) years, and 98 635 (75.5%) were White (Table). Of these, 120 803 certificates (92.5%) listed only illicit stimulants, 5544 (4.2%) listed only medical stimulants, and 3524 listed both types (2.7%). Among illicit stimulants, there were 77 013 deaths (61.9%) involving cocaine, 49 602 deaths (39.9%) involving methamphetamine, and 817 deaths (0.7%) involving 3,4 methylenedioxymethamphetamine. Among medical stimulants, there were 8240 deaths (90.9%) involving amphetamine, 295 deaths (0.3%) involving methylphenidate, and 615 deaths (0.7%) involving pseudoephedrine. Among all 3 stimulant groups, the proportion of deaths that also involved opioids was substantial; concomitant use of benzodiazepines and antidepressants was also not uncommon.

Stimulant mortality has risen rapidly since 2010 (Figure). The mortality rate involving all stimulants rose from 2.913 deaths per 100 000 population in 2010 to 9.690 in 2017. Mortality rates increased among all medical stimulants (ARR, 1.226; 95% CI, 1.202-1.250), amphetamine (ARR, 1.118; 95% CI, 1.082-1.155), cocaine (ARR, 1.234; 95% CI, 1.222-1.245), and methamphetamine (ARR, 1.278; 95% CI, 1.261-1.295).

Discussion | Our study showed an increase in mortality involving stimulants and identifies the substances that drive this upward trend. For many stimulants, there was a doubling in the mortality rate approximately every 4 years, which corresponds

Table. Demographic Characteristics of Decedents

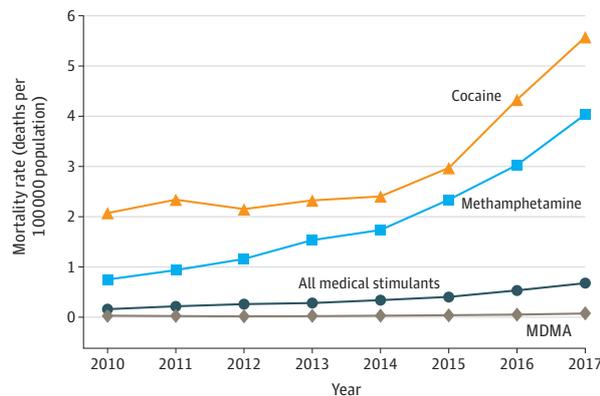
Characteristic	Deaths		Involving stimulants	
	All (n = 1 220 143)	Involving stimulants (n = 130 560)	Medical (n = 9115)	Illicit (n = 124 723)
Sex				
Women	414 839 (34.0)	36 871 (28.2)	3387 (37.2)	34 528 (27.7)
Men	805 304 (66.0)	93 689 (71.8)	5728 (62.8)	90 195 (72.3)
Age, median (IQR), y	55 (43-66)	45 (34-54)	40 (31-51)	45 (34-54)
Race ^a				
Asian or Pacific Islander	16 160 (1.3)	2487 (1.9)	177 (1.9)	2388 (1.9)
Black	127 928 (10.5)	27 215 (20.8)	381 (4.2)	26 978 (21.6)
Native American or Alaska Native	22 917 (1.9)	2223 (1.7)	159 (1.7)	2135 (1.7)
White	1 053 138 (86.3)	98 635 (75.5)	8398 (92.1)	93 222 (74.7)
Stimulant polysubstance deaths ^b				
With opioids	NA	56 988 (43.6)	4930 (54.1)	53 887 (43.2)
With benzodiazepines	NA	13 641 (10.4)	2447 (26.8)	11 960 (9.6)
With antidepressants	NA	4758 (3.6)	1207 (13.2)	3823 (3.1)

Abbreviations: CDC, US Centers for Disease Control and Prevention; IQR, interquartile range; NA, not applicable.

^a Standard CDC bridged race categories were used. Race was determined from entries on the death certificate.

^b Polysubstance deaths can involve more than 1 drug class; therefore, decedents could be in multiple categories.

Figure. Mortality Rates Involving Medical and Illicit Stimulants



Annual mortality rate (per 100 000 population) involving medical stimulants and select illicit stimulants. MDMA indicates 3,4 methylenedioxymethamphetamine.

to an ARR of 1.20. Stimulants are often used in combination with opioids and other drugs, as polysubstance use complicates treatment for use disorder. There are only 2 *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes for stimulants, and drugs listed by the medical certifier contain more information. Therefore, this study is more specific than studies that use *ICD* codes alone.^{3,4} The limitations of the study include that amphetamine is in the metabolic pathway of other stimulants, possibly producing misclassification, and the change in accuracy over time of identifying involved substances is not known.

The rapid rise in stimulant-involved mortality is concerning given the lack of tools to combat increasing mortality. To our knowledge, there are currently no medications approved to treat stimulant use disorder nor a reversal agent for stimulant-induced overdose. Opioid-involved mortality in 2000 had a similar rate (approximately 3 deaths per 100 000 population) and rose more slowly than our results have shown for stimulant-involved mortality.⁵ A notable difference is that stimulant-involved mortality predominantly stems from illicit drugs. These results should be a call to address stimulant-associated use before mortality reaches epidemic levels.

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