# Letters

RESEARCH LETTER

## Contribution of Opioid-Involved Poisoning to the Change in Life Expectancy in the United States, 2000-2015

Drug poisoning mortality more than doubled in the United States from 2000 to 2015; poisoning mortality involving opioids more than tripled.[1,2] Increases in poisonings have been reported to have reduced life expectancy for non-Hispanic white individuals in the United States from 2000 to 2014.[3] Specific contributions of drug, opioid, and alcohol poisonings to changes in US life expectancy since 2000 are unknown.

**Methods** | The number of deaths and death rates in 2000 and 2015 due to poisoning and the 12 leading causes of death in 2015 were estimated using the National Vital Statistics System Mortality file, based on death certificates registered in each state and the District of Columbia. The *International Classification of Diseases, Tenth Revision* (*ICD-10*), was used to classify cause of death.[4] In ranked cause-of-death classification, poisoning is not considered a unique cause. Poisoning deaths are classified as subsets of unintentional injuries, suicides, homicides, or events of undetermined intent.[4] *ICD-10* codes for specifically drug, opioid, or alcohol poisoning deaths were defined previously.[1,2,5]

Period life tables for the US population in 2000 and 2015 were calculated to estimate life expectancy by age. Life expectancy at any given age is the average number of years of life remaining for those surviving to that age, based on observed period death rates. Changes in life expectancy at birth were partitioned into component parts using the change in the proportion of deaths from specific causes for each age group for 2000 vs 2015.[4] Stata (StataCorp), version 13, was used to calculate life tables and Excel 2013 (Microsoft) for partitioning. The US Centers for Disease Control and Prevention determined the research was exempt from human subjects regulations because it used existing deidentified data.

**Results** | Life expectancy at birth increased by 2.0 years overall, rising from 76.8 years in 2000 to 78.8 years in 2015. From 2000 to 2015, death rates related to heart disease, cancer, cerebrovascular diseases, diabetes, influenza and pneumonia, chronic lower respiratory diseases, and kidney disease decreased (**Table**),

Table. Deaths and Age-Adjusted Death Rates for the Year 2000 vs 2015 for the 12 Leading Causes of Death and Drug, Opioid, Alcohol, and Other Poisoning Deaths in the United States

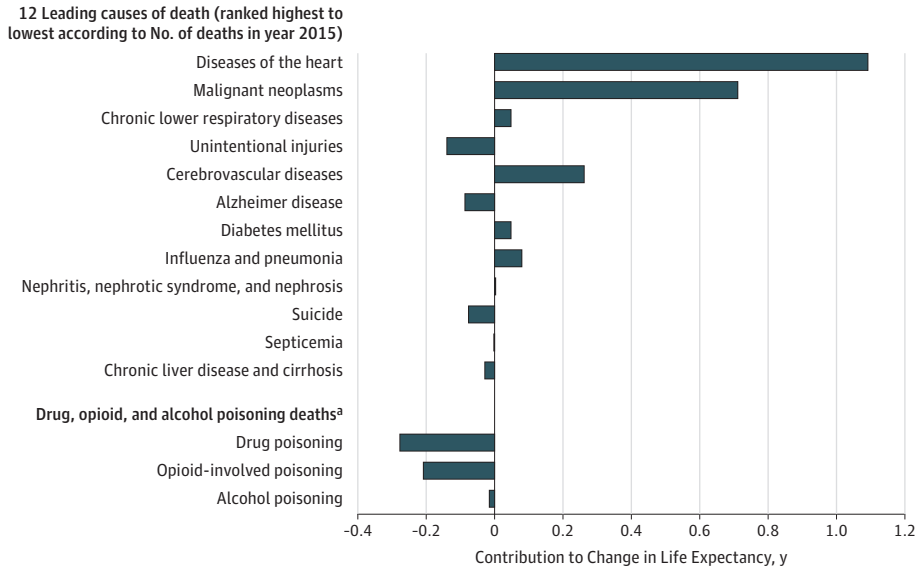
| | Year 2000 | | Year 2015 | | Change in Mortality Rate per 100 000 Population for 2000 vs 2015 (95% CI) |
|---|---|---|---|---|---|
| | Deaths, No. | Death Rate (95% CI)[a] | Deaths, No. | Death Rate (95% CI)[a] | |
| **12 Leading Causes of Death (Ranked Highest to Lowest According to No. of Deaths in Year 2015)** | | | | | |
| Diseases of the heart | 710 760 | 257.6 (257.0 to 258.2) | 633 842 | 168.5 (168.1 to 168.9) | −89.1 (−89.0 to −89.3) |
| Malignant neoplasms | 553 091 | 199.6 (199.1 to 200.2) | 595 930 | 158.5 (158.1 to 158.9) | −41.1 (−41.0 to −41.2) |
| Chronic lower respiratory diseases | 122 009 | 44.2 (43.9 to 44.4) | 155 041 | 41.6 (41.4 to 41.8) | −2.5 (−2.5 to −2.6) |
| Unintentional injuries | 97 900 | 34.9 (34.7 to 35.2) | 146 571 | 43.2 (43.0 to 43.4) | 8.3 (8.3 to 8.3) |
| Cerebrovascular diseases | 167 661 | 60.9 (60.6 to 61.2) | 140 323 | 37.6 (37.4 to 37.8) | −23.3 (−23.1 to −23.3) |
| Alzheimer disease | 49 558 | 18.1 (17.9 to 18.2) | 110 561 | 29.4 (29.3 to 29.6) | 11.4 (11.4 to 11.4) |
| Diabetes mellitus | 69 301 | 25.0 (24.9 to 25.2) | 79 535 | 21.3 (21.1 to 21.4) | −3.8 (−3.7 to −3.8) |
| Influenza and pneumonia | 65 313 | 23.7 (23.6 to 23.9) | 57 062 | 15.2 (15.1 to 15.4) | −8.5 (−8.4 to −8.6) |
| Nephritis, nephrotic syndrome, and nephrosis | 37 251 | 13.5 (13.4 to 13.6) | 49 959 | 13.4 (13.3 to 13.5) | −0.1 (−0.1 to −0.1) |
| Suicide | 29 350 | 10.4 (10.3 to 10.5) | 44 193 | 13.3 (13.2 to 13.4) | 2.9 (2.9 to 2.9) |
| Septicemia | 31 224 | 11.3 (11.2 to 11.4) | 40 773 | 11.0 (10.8 to 11.1) | −0.3 (−0.3 to −0.4) |
| Chronic liver disease and cirrhosis | 26 552 | 9.5 (9.4 to 9.7) | 40 326 | 10.8 (10.7 to 11.0) | 1.3 (1.3 to 1.3) |
| **Drug, Opioid, Alcohol, and Other Poisoning Deaths[b]** | | | | | |
| Drug poisoning | 17 415 | 6.2 (6.1 to 6.3) | 52 404 | 16.3 (16.2 to 16.4) | 10.1 (10.1 to 10.2) |
| Opioid | 8407 | 3.0 (2.9 to 3.0) | 33 091 | 10.4 (10.3 to 10.5) | 7.4 (7.3 to 7.4) |
| Other drug | 9008 | 3.2 (3.2 to 3.2) | 19 313 | 5.9 (5.9 to 5.9) | 2.7 (2.7 to 2.7) |
| Alcohol poisoning | 327 | 0.1 (0.1 to 0.1) | 2354 | 0.7 (0.7 to 0.7) | 0.6 (0.6 to 0.6) |
| Other poisoning | 2487 | 0.9 (0.9 to 0.9) | 2809 | 0.8 (0.8 to 0.9) | −0.1 (−0.1 to −0.1) |
| All poisonings[c] | 20 229 | 7.2 (7.1 to 7.3) | 57 567 | 17.8 (17.7 to 18.0) | 10.7 (10.6 to 10.7) |
| **Overall** | **2 403 351** | **869.0 (867.9 to 870.1)** | **2 712 630** | **733.1 (732.2 to 734.0)** | **−135.9 (−135.7 to −136.1)** |

[a] Age-adjusted rate per 100 000 population.

[b] Deaths may have involved multiple drugs or drugs and alcohol combined.

[c] Includes drug, alcohol, and other poisonings.

Figure. Contributions of Selected Causes of Death to the Change in Life Expectancy in the United States, 2000-2015




[a] In ranked cause-of-death classification, drug, opioid, and alcohol poisoning are not considered to be unique cause-of-death categories. Instead, poisoning deaths are classified as either accidental poisonings (which contribute to unintentional injuries), suicides, or homicides (ranked 16th in leading causes of death). Contributions from drug, opioid, and alcohol poisoning deaths overlap with both unintentional injury deaths and suicides and cannot be summed with these leading ranked causes of death.

together contributing a gain of 2.25 years to the change in life expectancy (**Figure**). Death rates related to unintentional injuries, Alzheimer disease, suicide, chronic liver disease, and septicemia increased (Table), together contributing a loss of 0.33 years to change in life expectancy (Figure).

Drug-poisoning deaths increased from 17 415 in 2000 to 52 404 in 2015; the age-adjusted death rate per 100 000 population increased from 6.2 to 16.3 (difference, 10.1 [95% CI, 10.1 to 10.2]), with most of the increase (7.4 [95% CI 7.3 to 7.4]) related to opioid deaths (Table). Drug-poisoning deaths contributed a loss of 0.28 years in life expectancy. Most of this loss (96%) was unintentional; 0.21 years were lost to opioid-involved poisoning deaths. Alcohol poisoning contributed a loss of 0.02 years (Figure).

**Discussion** | Between 2000 and 2015, life expectancy increased overall but drug-poisoning deaths contributed a loss of 0.28 years. This loss, mostly related to opioids, was similar in magnitude to losses from all the leading causes of death with increasing death rates during this period combined. Nearly all the life expectancy lost due to drug-poisoning deaths was unintentional and was therefore reflected in life lost to unintentional injury. However, unintentional injury appeared to account for less life lost than drug-poisoning deaths because of counterbalancing gains related to decreasing death rates from other unintentional injuries, particularly motor vehicle crashes.[3]

The finding for the contribution of opioid-involved poisoning deaths to the change in life expectancy is likely an underestimate because the accuracy and completeness of information recorded on death certificates affect cause-specific death rates. A specific drug is not recorded in as many as 25% of drug-poisoning deaths, although this percentage has modestly declined since 2010.

Increases in US life expectancy at birth have leveled off from a mean of 0.20 years gained annually from 1970 to 2000 to 0.15 years gained annually from 2000 to 2014.[4] US life expectancy decreased from 2014 to 2015 and is now lower than in most high-income countries, with this gap projected to increase.[6] These findings suggest that preventing opioid-related poisoning deaths will be important to achieving more robust increases in life expectancy once again.

**Deborah Dowell, MD, MPH**
**Elizabeth Arias, PhD**
**Kenneth Kochanek, MA**
**Robert Anderson, PhD**
**Gery P. Guy Jr, PhD, MPH**
**Jan L. Losby, PhD, MSW**
**Grant Baldwin, PhD, MPH**

**Author Affiliations:** National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, Atlanta, Georgia (Dowell, Guy, Losby, Baldwin); National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland (Arias, Kochanek, Anderson).

**Accepted for Publication:** June 23, 2017.

**Corresponding Author:** Deborah Dowell, MD, MPH, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, 4770 Buford Hwy NE, MS F-62, Atlanta, GA 30341 (ddowell@cdc.gov).

**Author Contributions:** Drs Dowell and Arias had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design:* Dowell, Arias, Guy, Losby.
*Acquisition, analysis, or interpretation of data:* Dowell, Arias, Kochanek, Anderson, Guy, Baldwin.
*Drafting of the manuscript:* Dowell, Arias, Baldwin.
*Critical revision of the manuscript for important intellectual content:* All authors.
*Statistical analysis:* Arias, Kochanek, Anderson, Guy.
*Administrative, technical, or material support:* Losby, Baldwin.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

**Disclaimer:** The views expressed in this article are those of the authors and do not necessarily reflect the official position of the US Centers for Disease Control and Prevention.


1. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths—United States, 2000-2014. *MMWR Morb Mortal Wkly Rep*. 2016;64(50-51):1378-1382.

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. Kochanek KD, Arias E, Bastian BA. National Center for Health Statistics: the effect of changes in selected age-specific causes of death on non-Hispanic white life expectancy between 2000 and 2014. https://www.cdc.gov/nchs/products/databriefs/db250.htm. Accessed August 1, 2017.

4. Kochanek KD, Murphy SL, Xu J, Tejada-Vera B. National Vital Statistics Reports: deaths: final data for 2014. https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_04.pdf. Accessed August 1, 2017.

5. Kanny D, Brewer RD, Mesnick JB, Paulozzi LJ, Naimi TS, Lu H. Vital signs: alcohol poisoning deaths—United States, 2010-2012. *MMWR Morb Mortal Wkly Rep*. 2015;63(53):1238-1242.

6. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialized countries: projections with a Bayesian model ensemble. *Lancet*. 2017 389(10076):1323-1335.


## COMMENT & RESPONSE

### Characteristics of Novel Therapeutics and Postmarket Safety Events

**To the Editor** Dr Downing and colleagues[1] analyzed the frequency of postmarket safety events among 222 novel therapeutics approved by the US Food and Drug Administration (FDA) between 2001 and 2010 and found that 32% had a postmarket safety event during a median 11.7 years after approval. The authors prespecified 7 features to assess for differences in events over time: (1) class, (2) therapeutic area, (3) priority review, (4) accelerated approval, (5) orphan product, (6) near-regulatory deadline approval, and (7) total review time. However, we would like to raise additional features that need further consideration to interpret the study results.

First, the length of treatment might be associated with the frequency of postmarket safety events (ie, drugs administered only for limited times or those administered continuously for a longer period). Unrecognized safety events would be more likely with drugs administered for a longer time.

Second, the authors previously compared the regulatory review process for novel therapeutics among the FDA, the European Medicines Agency (EMA), and Health Canada from 2001 through 2010. Among the 289 unique novel therapeutic agents, 190 were approved in both the United States and Europe, of which 69 (36.3%) were first approved in Europe; 154 were approved in both the United States and Canada, of which 22 (14.3%) were first approved in Canada.[2] In the case of novel therapeutics that were first approved by other regulatory authorities, it is conceivable that more safety information had already been accumulated at the time of the US approval compared with those that were first approved in the United States, leading to fewer postmarket safety events.

Third, the precision and accuracy of submitted data of pivotal clinical trials for regulatory approval, such as the size of the trial and the length of follow-up, could matter. The authors previously reported that the precision and accuracy of clinical trial evidence used by the FDA varied widely; among 188 novel therapeutics for 206 indications approved between 2005 and 2012, the median number of patients enrolled per indication among all pivotal trials was 760 (interquartile range, 270-1550), and at least 1 pivotal trial with a duration of 6 months or greater supported the approval of 68 indications (33.8%).[3] If the minimum requirements for the size and the duration of pivotal clinical trials that might lead to fewer postmarket safety events could be characterized, it would contribute to development of regulatory strategies for novel therapeutics.


**Tetsuya Tanimoto, MD**
**Jinichi Mori, MD, PhD**
**Yasuo Oshima, MD, PhD**

**Author Affiliations:** Jyoban Hospital of Tokiwa Foundation, Fukushima, Japan (Tanimoto, Mori); Institute of Medical Sciences, University of Tokyo, Tokyo, Japan (Oshima).

**Corresponding Author:** Tetsuya Tanimoto, MD, Jyoban Hospital of Tokiwa Foundation, 9728322 Fukushima, Japan (tetanimot@yahoo.co.jp).



**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Oshima reported receiving personal fees from Novartis Pharma K. K. and owning stock in Sanofi K. K. No other disclosures were reported.



1. Downing NS, Shah ND, Aminawung JA, et al. Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010. *JAMA*. 2017;317(18):1854-1863.

2. Downing NS, Aminawung JA, Shah ND, Braunstein JB, Krumholz HM, Ross JS. Regulatory review of novel therapeutics—comparison of three regulatory agencies. *N Engl J Med*. 2012;366(24):2284-2293.

3. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. *JAMA*. 2014;311(4):368-377.


**In Reply** Dr Tanimoto and colleagues suggest that 3 additional characteristics of novel therapeutics or features of their regulatory approval should be considered when examining potential predictors of postmarket safety events after approval by the FDA: expected length of treatment, first approval by a peer regulator, such as the EMA, and total number of patients participating in the manufacturer's pivotal trial program. We appreciate these suggestions and in response have examined whether postmarket safety event risk was associated with either expected length of treatment or relative number of patients participating in premarket clinical studies. However, we did not examine first approval by a peer regulator because new drug application submission occurs more or less simultaneously to the FDA and EMA, with approval within a few months.[1]

Using a previously described framework to characterize expected length of treatment,[2] we determined that, among novel therapeutics approved by the FDA between 2001 and 2010 that were the basis of our original study, 41 (18.5%) were expected to be used for short-term treatment, 51 (23.0%) for intermediate periods, and 130 (58.6%) for long-term treatment.

Because the number of patients participating in premarket clinical studies will be influenced by disease prevalence, for each non-orphan-designated therapeutic, we estimated the relative, as opposed to the absolute, size of the premarket clinical development program. To do this, we first used the Drugs@FDA database to determine the total number of