PLOS ONE

RESEARCH ARTICLE

Rise in mortality involving poisoning by medicaments other than narcotics, including poisoning by psychotropic drugs in different age/racial groups in the US

Edward Goldstein *

Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, United States of America

* egoldste@hsph.harvard.edu

Citation: Goldstein E (2019) Rise in mortality involving poisoning by medicaments other than narcotics, including poisoning by psychotropic drugs in different age/racial groups in the US. PLoS ONE 14(7): e0219711. https://doi.org/10.1371/journal.pone.0219711

Editor: Hajo Zeeb, Leibniz Institute for Prevention Research and Epidemiology BIPS, GERMANY

Received: March 5, 2019

Accepted: June 29, 2019

Published: July 19, 2019

Data Availability Statement: We utilize the publicly available US CDC Wonder data on death/population counts (estimates), available through ref. 30 (https://wonder.cdc.gov/wonder/help/ucd.html).

Funding: This study involves no funding.

Competing interests: Edward Goldstein is on editorial board for PLOS ONE. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Abstract

Background

Increase in mortality involving poisoning, particularly by narcotics, is known to have been one of the factors that affected life expectancy in the US during the last two decades, especially for white Americans and Native Americans. However, the contribution of medicaments other than narcotics to mortality in different racial/age groups is less studied.

Methods

We regressed annual rates of mortality involving poisoning by medicaments but not narcotics/psychodysleptics (ICD-10 codes T36-39.xx or T41-50.8 but not T40.xx present as either underlying or contributing causes of death), as well as annual rates of mortality for certain subcategories of the above, including mortality involving poisoning by psychotropic drugs but not narcotics/psychodysleptics (ICD-10 codes T43.xx but not T40.xx present as either underlying or contributing causes of death) in different age/racial groups for both the 2000–2011 period and the 2011–2017 period against calendar year.

Results

Annual numbers of deaths involving poisoning by medicaments but not narcotics/psychodysleptics grew from 4,332 between 2000–2001 to 11,401 between 2016–2017, with the growth in the rates of those deaths being higher for the 2011–2017 period compared to the 2000–2011 period. The largest increases in the rates of mortality involving poisoning by medicaments but not narcotics/psychodysleptics were in non-elderly Non-Hispanic Native Americans, followed by Non-Hispanic whites. Most of those increases came from increases in the rates of mortality involving poisoning by psychotropic medications; the latter rates grew for the period of 2015–2017 vs. 2000–2002 by factors ranging from 2.75 for ages 35-44y to 5.37 for ages 55-64y.

Conclusions

There were major increases in mortality involving poisoning by non-narcotic, particularly psychotropic medicaments, especially in non-elderly non-Hispanic whites and Native Americans. Our results support the need for a comprehensive evaluation of the effect of psychotropic medications on health-related outcomes, including mortality for causes other than poisoning, and the impact of medication misuse.

Introduction

During the last two decades, life expectancy in white Americans has been decreasing compared to other major racial groups. By 2006, life expectancy in Hispanics became about 2.1 years higher than in non-Hispanic whites; by 2014, that gap has grown to about 3.2 years (Fig 4 in ref. [1]). Life expectancy in African Americans is consistently lower than in whites, though the gap has been decreasing significantly in the recent years (Fig 4 in ref. [2]; Fig 4 in ref. [1]). In absolute terms, life expectancy in whites has been declining starting 2014 [1,3], together with the overall decline in life expectancy in the US starting 2015 [4] amid an ongoing epidemic of drug overdose deaths [5,6].

Several factors behind the relative decline in life expectancy in white Americans have been proposed, [4,7]. In particular, as suggested by a study that compared midlife mortality for the 2013–2015 period vs. the 1999–2001 period [8], increases in mortality by poisoning, suicide, and liver disease in non-elderly white Americans were notably higher compared to Hispanics and blacks. Moreover, those increases, particularly for deaths by poisoning, took place in both the urban/suburban and rural areas (Fig 1 in ref. [8]). While the use of narcotics [5,6] is known to be a contributor to the long-term trends in the rates of midlife mortality by poisoning and drug overdose [9,8], misuse of medicaments other than narcotics may also have a pernicious health-related effect, including contribution to mortality in different population groups, particularly white Americans and Native Americans [9]. We note that the rates of consumption of certain medicaments in white Americans are higher than in other racial groups (excluding Native Americans) [10]. In particular, there are major differences in the rates of consumption of antibiotics [11,12], psychotropic drugs [13], including antidepressants [14,15], and sedative-hypnotic medications [16–18] between white Americans and other racial groups in the US except Native Americans. A number of studies, including meta-analyses, suggest elevated risks for mortality, including sudden cardiac death (SCD) associated with the use of various psychotropic drugs (both antipsychotics and antidepressants), as well as certain sedative-hypnotic drugs (benzodiazepines) [19–24], though firmly establishing causal links in such studies can be challenging [25]. For the case of antibiotics, recent work suggests an association between prescribing rates for certain antibiotics, particularly penicillins in the elderly, and mortality and hospitalization rates for sepsis/septicemia [26,27], with that association presumably being mediated by antimicrobial resistance [28]. Further work is needed to gain a more comprehensive understanding of the effect of prescribing and misuse of different medications on health-related, including mortality outcomes in different age/racial groups.

In this paper, we study one of the more direct types of contribution of medication use to mortality, namely mortality that involves poisoning by medications. We note that the rise in the rates of mortality associated with narcotic, including opiate overdose is well-documented, e.g. [5,6,9]. However, trends in mortality involving poisoning by various medicaments other than narcotics in the US are apparently not well studied. Here, we utilized the US CDC

Wonder mortality database [29] to examine trends in mortality involving poisoning by medicaments other than narcotics/psychodysleptics in different age/racial groups in the US, including trends in mortality rates for certain subcategories of those deaths, particularly deaths involving poisoning by psychotropic, as well as sedative-hypnotic drugs. Our aim is to characterize the volume of such deaths, as well as trends in the rates of those deaths in different age/racial groups during different time periods. This initial analysis is meant to provide rationale for further study of the contribution of medication use to mortality outcomes, including mortality that does not involve poisoning by medicaments present on the death certificate (e.g. [19–25]).

Methods

Data

We have extracted annual mortality data between 2000–2017 stratified by age group (25-34y, 35-44y, 45-54y, 55-64y, 65-74y) and racial group (Hispanics, Non-Hispanic whites, Non-Hispanic blacks, Non-Hispanic Asian-Americans, Non-Hispanic Native Americans) from the US CDC Wonder database [29]. Those data may be freely and publicly downloaded at the URL provided. While the 1999 data are also available in ref. [29], the 1999 mortality rates in the various categories that we have considered are generally higher than those rates during the subsequent years, possibly having to do with the transition from ICD-9 to ICD-10 coding around that time [30] and other factors relating to coding; correspondingly, the 1999 data were excluded from our analyses. The mortality data between 2000–2017 were extracted for five types of deaths:

Type 1. Deaths involving poisoning by drugs, medicaments, and other biological substances: ICD-10 codes T36-50.xx present as either underlying or contributing causes of death

Type 2. Deaths involving poisoning by narcotics and psychodysleptics: ICD-10 codes T40.xx present as either underlying or contributing causes of death

Type 3. Deaths involving poisoning by specific drugs, medicaments, and other biological substances: ICD-10 codes T36-50.8 present as either underlying or contributing causes of death. We note that ICD-10 codes T50.9 represent poisoning by other and unspecified drugs, medicaments, and other biological substances, and those deaths are not included in type 3.

Type 4. Deaths involving poisoning by either psychotropic drugs (antipsychotic/neuroleptic drugs and antidepressants) or narcotics and psychodysleptics: ICD-10 codes T43.xx or T40.xx present as either underlying or contributing causes of death

Type 5. Deaths involving poisoning by either sedative-hypnotic drugs (barbiturates and benzodiazepines) or narcotics and psychodysleptics: ICD-10 codes T42.3–43.4 or T40.xx present as either underlying or contributing causes of death

Those data were used to calculate the mortality rates for different categories of death used in this study. Those categories, and the calculation of the corresponding mortality rates are described in Table 1 below.

We note that the reason behind the subtraction for categories C-E is that if one wants to find the number of deaths that have causes X but not Y (e.g. psychotropic medications but not narcotics/psychodysleptics) listed on the death certificate, one subtracts the number of deaths that have causes Y listed on a death certificate from the number of deaths that have either causes X or causes Y listed on a death certificate.

Trends in mortality rates (regression analysis)

For each age/racial group, we have regressed the corresponding annual rates of mortality for categories A through E (Table 1) against the calendar year covariate (univariate regression).

Table 1. Different categories of death used in the analyses, and the relevant ICD-10 reflecting either the underlying or contributing causes of death.

Category	Description	ICD-10 (underlying or contributing)	Extraction process
A	Poisoning by drugs, medicaments, and other biological substances	T36-50.xx	Rates in type 1 in the Methods
B	Poisoning by narcotics and psychodysleptics	T40.xx	Rates in type 2 in the Methods
C	Poisoning by medicaments but not narcotics and psychodysleptics	T36-39.xx or T41-50.8 but not T40.xx	Rates in type 2 subtracted from rates in type 3 in the Methods
D	Poisoning by psychotropic drugs but not narcotics and psychodysleptics	T43.xx but not T40.xx	Rates in type 2 subtracted from rates in type 4 in the Methods
E	Poisoning by sedative-hypnotic drugs but not narcotics and psychodysleptics	T42.3–42.4 but not T40.xx	Rates in type 2 subtracted from rates in type 5 in the Methods

https://doi.org/10.1371/journal.pone.0219711.t001

Given the apparent change in the trends for mortality involving poisoning by medicaments (including psychotropic drugs) but not narcotics and psychodysleptics in certain age/racial groups starting around 2012, the regression analyses were performed separately for the 2000–2011 period and the 2011–2017 period. The regression coefficient for the calendar year covariate estimates the annual increase in the rate of mortality for the corresponding category (A. through E. in Table 1) in the given age/racial group during the corresponding time period (2000–2011 or 2011–2017).

Relative changes in mortality rates

In addition to the evaluation of trends in mortality for the different categories of death (listed in Table 1) in different age/racial groups, we also calculated the relative (fold) increases in the rates of mortality for categories B, C, D, E in Table 1 in different age groups of US adults. We considered, for different age groups of adults and categories B through E, changes in average annual mortality rates for the 2015–2017 period vs. 2000–2002 period, as well as for the 2011–2014 period vs. 2000–2002 period (with the latter relative change evaluated to allow for the comparison with changes in prescribing rates for different medications during the same period recorded in ref. [31]).

Spatial variability in the rates of mortality involving poisoning by different substances

In addition to temporal changes in the rates of mortality involving poisoning by different substances, we also looked at state-specific rates of mortality involving poisoning by psychotropic drugs but not narcotics/psychodysleptics (category D in Table 1), as well as mortality involving poisoning by narcotics/psychodysleptics (category B in Table 1), including correlations between those state-specific rates.

Results

Figs 1–5 plot the annual rates of mortality (per 100,000 individuals) between 2000–2017 for the different categories of death (A through E) in Table 1. For the younger age groups (ages 25-34y, 35-44y and 45-54y), the largest increases in mortality rates for all the categories A-E were in non-Hispanic Native Americans, followed by non-Hispanic whites. Fig 1 plots the annual rates of mortality involving poisoning by drugs, medicaments, and other biological substances (category A in Table 1) between 2000–2017 for the different age/racial groups. Fig 2 plots the annual rates of mortality involving poisoning by narcotics and psychodysleptics (category B in Table 1) between 2000–2017 for the different age/racial groups. We note that

Rates of mortality (per 100,000) involving poisoning by drugs, medicaments and other biological substances

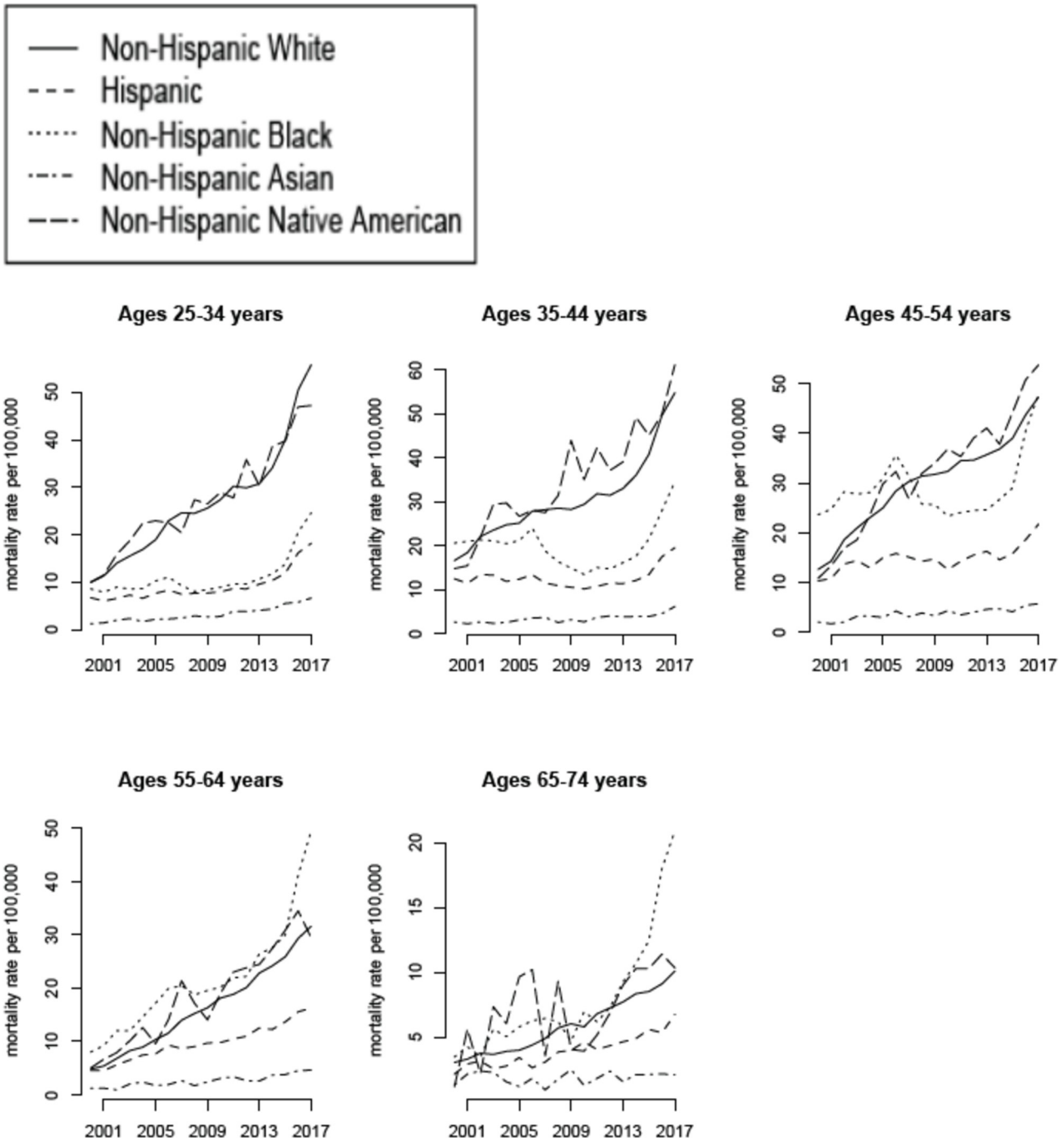

Fig 1. Annual rates of mortality involving poisoning by drugs, medicaments and other biological substances (ICD-10 codes T36-50.xx present as either underlying or contributing causes of death; category A in Table 1) between 2000–2017 per 100,000 individuals in different age/racial groups.

https://doi.org/10.1371/journal.pone.0219711.g001

Rates of mortality (per 100,000) involving poisoning by narcotics and psychodysleptics

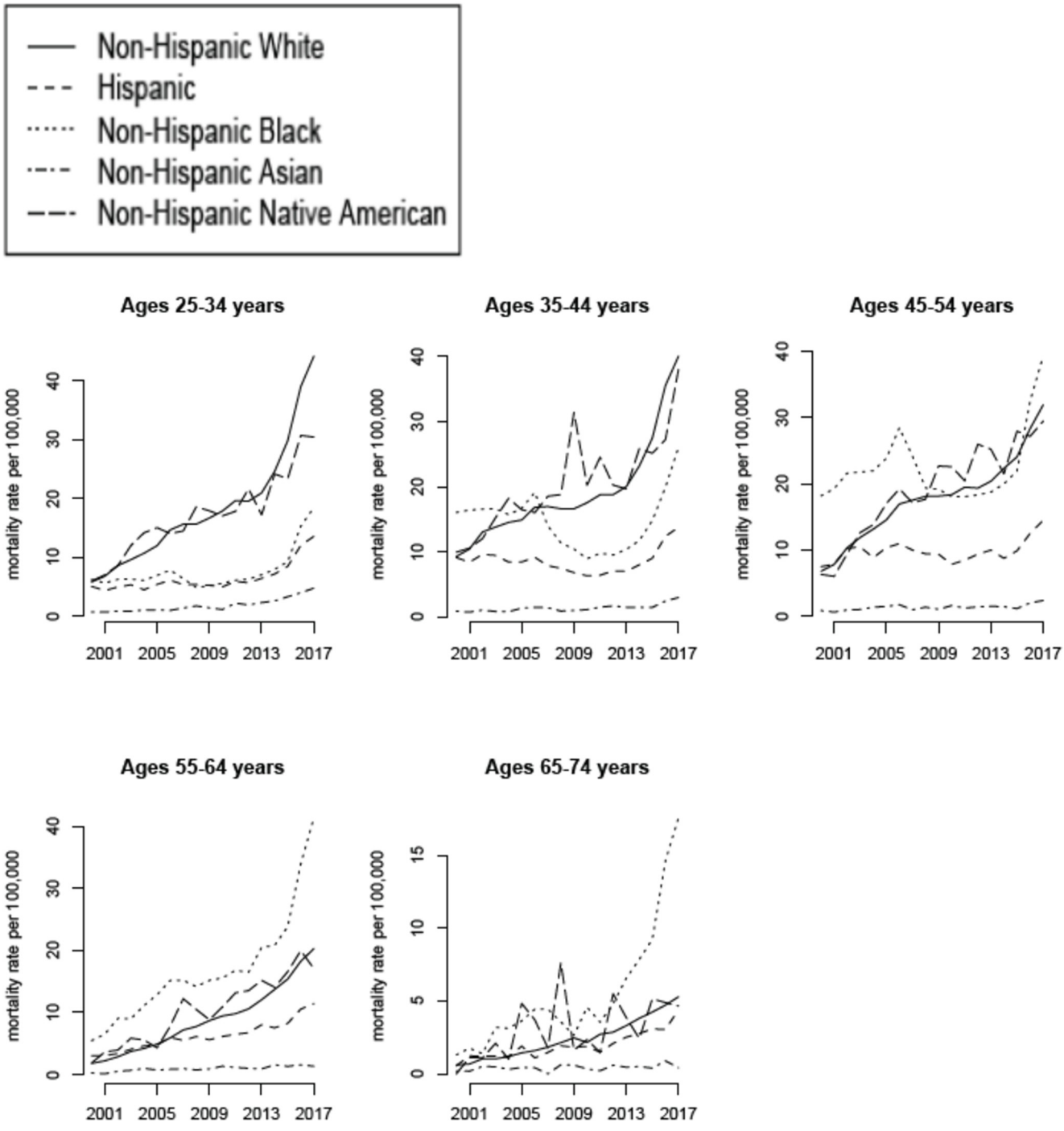

Fig 2. Annual rates of mortality involving poisoning by narcotics and psychodysleptics (ICD-10 codes T40.xx present as either underlying or contributing causes of death; category B in Table 1) between 2000–2017 per 100,000 individuals in different age/racial groups.

https://doi.org/10.1371/journal.pone.0219711.g002

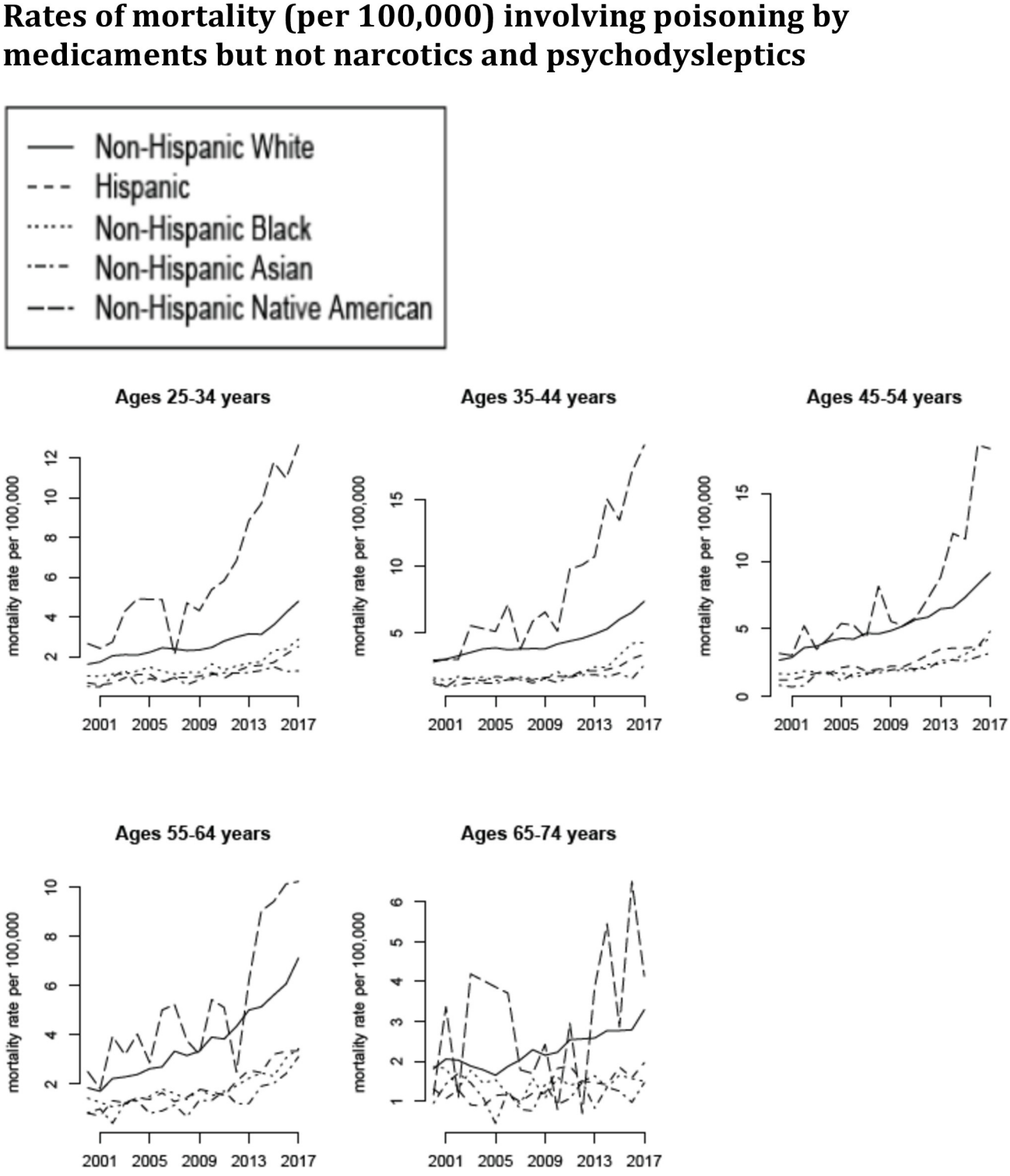

Fig 3. Annual rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics (ICD-10 codes T36-39.xx or T41-50.8 but not T40.xx not present as either underlying or contributing causes of death; category C in Table 1) between 2000–2017 per 100,000 individuals in different age/racial groups.

https://doi.org/10.1371/journal.pone.0219711.g003

Rates of mortality (per 100,000) involving poisoning by psychotropic drugs but not narcotics and psychodysleptics

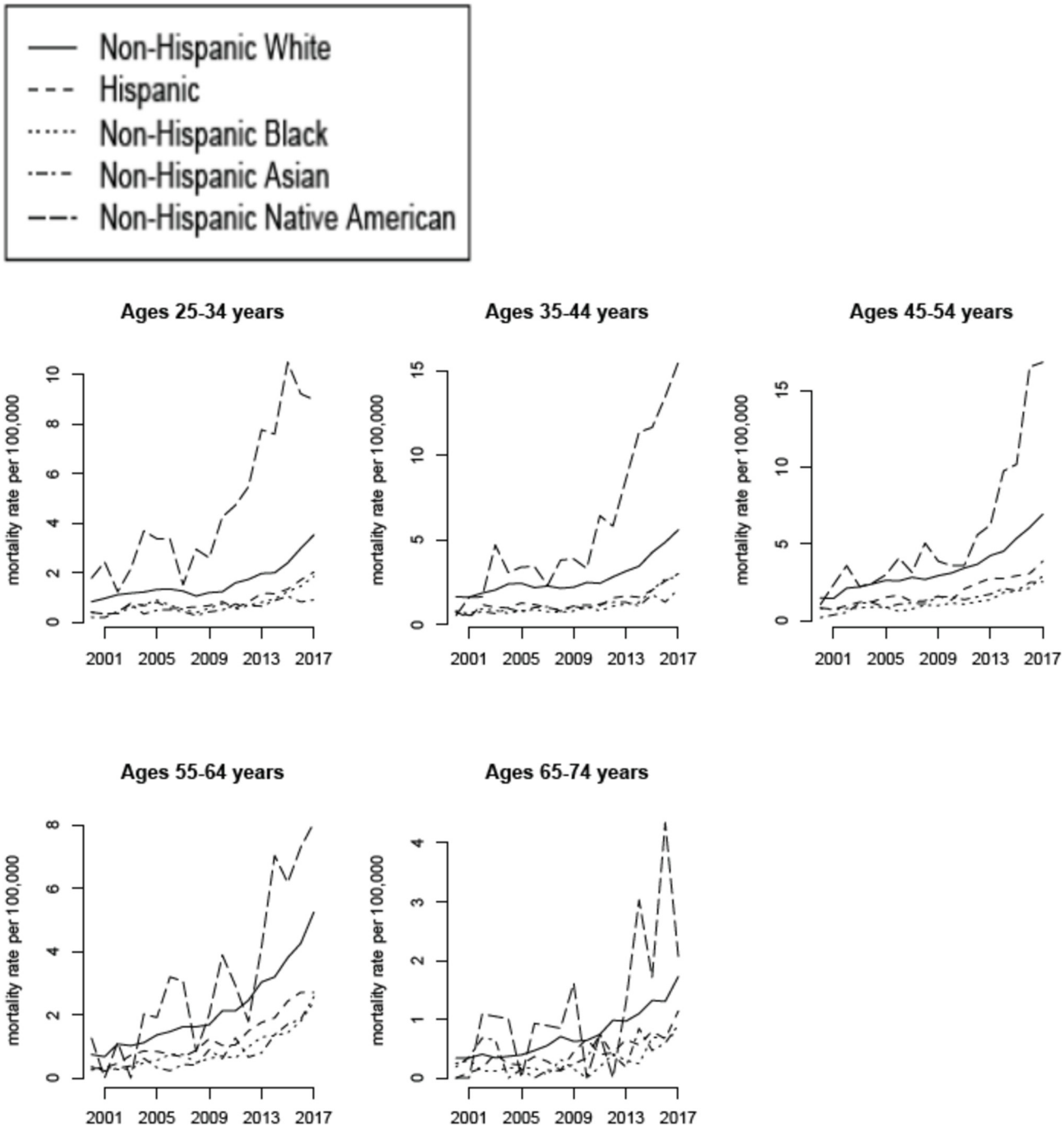

Fig 4. Annual rates of mortality involving poisoning by psychotropic drugs but not narcotics and psychodysleptics (ICD-10 codes T43.xx but not T40.xx not present as either underlying or contributing causes of death; category D in Table 1) between 2000–2017 per 100,000 individuals in different age/racial groups.

https://doi.org/10.1371/journal.pone.0219711.g004

Rates of mortality (per 100,000) involving poisoning by sedative-hypnotic drugs (barbiturates or benzodiazepines) but not narcotics and psychodysleptics

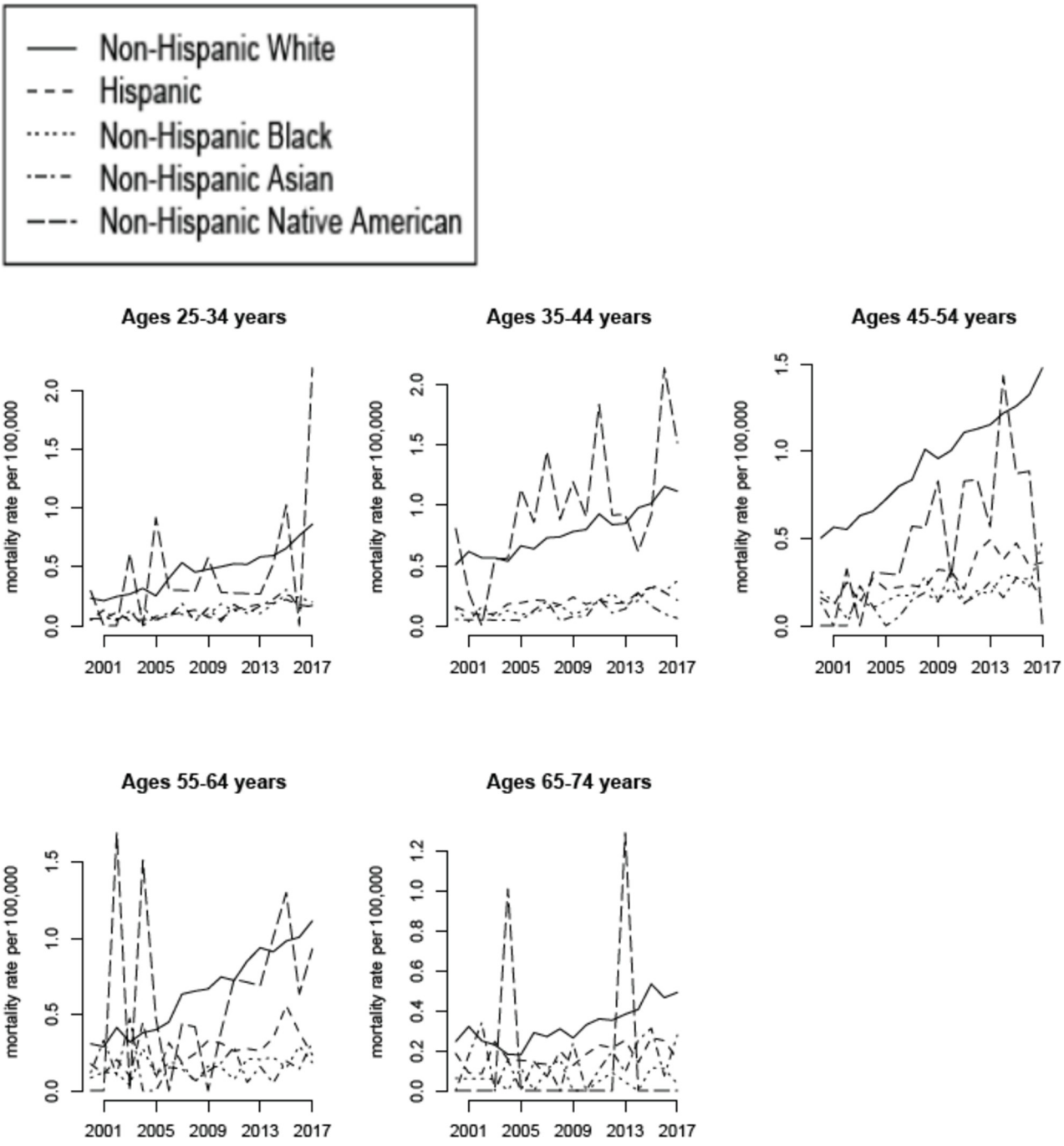

Fig 5. Annual rates of mortality involving poisoning by sedative-hypnotic drugs but not narcotics and psychodysleptics (ICD-10 codes T42.3–42.4 but not T40.xx not present as either underlying or contributing causes of death; category E in Table 1) between 2000–2017 per 100,000 individuals in different age/racial groups.

https://doi.org/10.1371/journal.pone.0219711.g005

Table 2. Annual change in mortality rates involving poisoning by medicaments but not narcotics and psychodysleptics (ICD-10 codes T36-39.xx or T41-50.8 but not T40.xx not present as either underlying or contributing causes of death; category C in Table 1) between 2000–2011 and between 2011–2017 per 100,000 individuals in different age/racial groups.

2000–2011 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**0.08 (0.06,0.1)**	**0.11 (0.08,0.14)**	**0.24 (0.21,0.27)**	**0.20 (0.17,0.23)**	**0.05 (0.02,0.08)**
Hispanics	**0.03 (0.01,0.06)**	**0.05 (0.02,0.07)**	**0.11 (0.08,0.14)**	**0.07 (0.04,0.11)**	**0.05 (0.01,0.1)**
Non-Hispanic blacks	**0.03 (0.01,0.06)**	0.02 (-0.01,0.05)	0.02 (-0.01,0.05)	**0.04 (0.01,0.07)**	-0.04 (-0.09,0)
Non-Hispanic Asian Americans	0.03 (-0.01,0.08)	**0.04 (0.01,0.06)**	**0.12 (0.08,0.17)**	**0.06 (0.01,0.11)**	-0.03 (-0.09,0.03)
Non-Hispanic Native Americans	**0.23 (0.07,0.4)**	**0.41 (0.18,0.64)**	**0.26 (0.08,0.44)**	**0.23 (0.08,0.37)**	-0.05 (-0.26,0.17)
2011–2017 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**0.32 (0.22,0.42)**	**0.50 (0.41,0.59)**	**0.58 (0.45,0.7)**	**0.50 (0.41,0.58)**	**0.10 (0.05,0.16)**
Hispanics	**0.24 (0.19,0.29)**	**0.26 (0.19,0.33)**	**0.28 (0.17,0.4)**	**0.30 (0.22,0.38)**	0.03 (-0.06,0.12)
Non-Hispanic blacks	**0.25 (0.19,0.31)**	**0.47 (0.37,0.58)**	**0.38 (0.29,0.46)**	**0.28 (0.21,0.36)**	0.02 (-0.03,0.06)
Non-Hispanic Asian Americans	0.03 (-0.01,0.06)	0.08 (-0.04,0.2)	**0.19 (0.12,0.25)**	**0.27 (0.12,0.41)**	0.02 (-0.08,0.12)
Non-Hispanic Native Americans	**1.13 (0.87,1.39)**	**1.6 (1.12,2.08)**	**2.25 (1.67,2.83)**	**1.21 (0.64,1.78)**	0.51 (-0.12,1.13)

https://doi.org/10.1371/journal.pone.0219711.t002

most deaths involving poisoning by drugs, medicaments, and other biological substances are deaths involving poisoning by narcotics and psychodysleptics (Figs 2 vs. 1). Rates of mortality involving poisoning by narcotics and psychodysleptics in white and Native Americans aged under 55y are high. For example, for Non-Hispanic whites, by 2017 about a third of all deaths in individual aged 25-34y, and about 20% of all deaths in individuals aged 35-44y involved poisoning by narcotics and psychodysleptics. The largest rises in mortality rates involving poisoning by narcotics and psychodysleptics in older age groups (55-64y and 65-74y), particularly during the most recent years, were in non-Hispanic blacks (Fig 2).

The number of deaths involving poisoning by medicaments but not narcotics and psychodysleptics in the US increased significantly during our study period, from the annual average of 4,332 between 2000–2001 to the annual average of 11,401 between 2016–2017. Fig 3 plots the annual rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics (category C in Table 1) between 2000–2017 for the different age/racial groups. We note that those rates are lower than the rates of mortality involving poisoning by narcotics and psychodysleptics (Fig 3 vs. Fig 2). Figs 4 and 5 plot the annual rates of mortality involving poisoning by psychotropic drugs but not narcotics and psychodysleptics (category D in Table 1) and sedative-hypnotic drugs but not narcotics and psychodysleptics (category E in Table 1) between 2000–2017 for the different age/racial groups. The majority of deaths involving poisoning by medicaments but not narcotics and psychodysleptics, as well as most of the increases in those death rates were for deaths involving poisoning by psychotropic drugs but not narcotics and psychodysleptics (Figs 3 vs. 4).

Table 3. Annual change in mortality rates involving poisoning by psychotropic drugs but not narcotics and psychodysleptics (ICD-10 codes T43.xx but not T40.xx present as either underlying or contributing causes of death; category D in Table 1) between 2000–2011 and between 2011–2017 per 100,000 individuals in different age/racial groups.

2000–2011 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**0.04 (0.01,0.06)**	**0.07 (0.03,0.1)**	**0.16 (0.13,0.19)**	**0.13 (0.11,0.15)**	**0.04 (0.03,0.05)**
Hispanics	**0.03 (0,0.05)**	0.03 (0,0.07)	**0.08 (0.05,0.12)**	**0.07 (0.05,0.09)**	**0.04 (0.01,0.06)**
Non-Hispanic blacks	0.02 (-0.01,0.04)	0.01 (-0.01,0.03)	**0.03 (0.01,0.05)**	**0.04 (0.02,0.06)**	-0.01 (-0.02,0.01)
Non-Hispanic Asian Americans	0.02 (0,0.05)	**0.04 (0.02,0.06)**	**0.11 (0.07,0.14)**	**0.06 (0.02,0.1)**	0 (-0.04,0.05)
Non-Hispanic Native Americans	**0.20 (0.05,0.34)**	**0.31 (0.13,0.5)**	**0.20 (0.08,0.33)**	**0.24 (0.08,0.4)**	0.04 (-0.05,0.13)
2011–2017 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**0.31 (0.22,0.4)**	**0.52 (0.44,0.61)**	**0.59 (0.49,0.68)**	**0.49 (0.41,0.57)**	**0.14 (0.1,0.18)**
Hispanics	**0.22 (0.19,0.26)**	**0.29 (0.21,0.36)**	**0.24 (0.17,0.32)**	**0.29 (0.24,0.34)**	**0.10 (0.05,0.15)**
Non-Hispanic blacks	**0.21 (0.18,0.25)**	**0.36 (0.27,0.45)**	**0.28 (0.21,0.35)**	**0.25 (0.19,0.32)**	**0.10 (0.05,0.15)**
Non-Hispanic Asian Americans	0.04 (0,0.09)	**0.11 (0.01,0.22)**	**0.20 (0.15,0.25)**	**0.26 (0.12,0.4)**	0.04 (-0.06,0.14)
Non-Hispanic Native Americans	**0.82 (0.4,1.25)**	**1.62 (1.3,1.95)**	**2.34 (1.81,2.87)**	**1.02 (0.62,1.42)**	**0.47 (0.05,0.89)**

https://doi.org/10.1371/journal.pone.0219711.t003

Figs 3 and 4 suggest an apparent change in the trends for mortality involving poisoning by medicaments (including psychotropic drugs) but not narcotics and psychodysleptics in certain age/racial groups (particularly Non-Hispanic Native Americans, Non-Hispanic whites and Hispanics aged 25-44y) starting around 2012. Table 2 gives the estimates of the annual increase in the rate of mortality involving poisoning by medicaments but not narcotics and psychodysleptics in different age/racial groups between 2000–2011, as well as between 2011–2017 (see the *Trends in mortality rates (regression analysis)* subsection of the Methods). The corresponding estimates for mortality involving poisoning by psychotropic and sedative-hypnotic medications are presented in Tables 3 and 4. Annual increases in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics between 2011–2017 are significantly higher than the corresponding increases during the 2000–2011 period, with the largest relative change between the two time periods being in Non-Hispanic blacks. The greatest increases in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics during each time period are in non-elderly Non-Hispanic Native Americans, followed by Non-Hispanic whites.

Table 5 presents the estimates of annual increases in mortality rates involving poisoning by narcotics and psychodysleptics between 2000–2011, as well as between 2011–2017. Some of the largest increases in those rates are notably higher than the increases in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics (Tables 5 vs. 2). For the 2000–2011 period, for younger age groups (25-54y), the largest increases in mortality rates involving poisoning by narcotics and psychodysleptics were in

Table 4. Annual change in mortality rates involving poisoning by sedative-hypnotic drugs but not narcotics and psychodysleptics (ICD-10 codes T42.3–42.4 but not T40.xx present as either underlying or contributing causes of death; category E in Table 1) between 2000–2011 and between 2011–2017 per 100,000 individuals in different age/racial groups.

2000–2011 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**0.03 (0.02,0.04)**	**0.03 (0.02,0.04)**	**0.06 (0.05,0.06)**	**0.05 (0.04,0.06)**	0.01 (0,0.02)
Hispanics	0 (0,0.01)	**0.01 (0,0.02)**	**0.01 (0,0.02)**	0.01 (0,0.03)	0 (-0.01,0.01)
Non-Hispanic blacks	**0.01 (0,0.01)**	0.01 (0,0.01)	0.01 (0,0.02)	0 (-0.01,0.01)	0 (-0.01,0.01)
Non-Hispanic Asian Americans	0.01 (-0.01,0.02)	**0.01 (0,0.02)**	0.01 (0,0.03)	0 (-0.03,0.02)	0 (-0.02,0.02)
Non-Hispanic Native Americans	0.02 (-0.03,0.06)	**0.10 (0.04,0.16)**	**0.07 (0.04,0.09)**	-0.01 (-0.11,0.09)	-0.01 (-0.06,0.04)
2011–2017 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**0.06 (0.04,0.07)**	**0.05 (0.02,0.07)**	**0.06 (0.04,0.07)**	**0.05 (0.04,0.07)**	**0.03 (0.01,0.04)**
Hispanics	0 (-0.01,0.01)	0.01 (-0.01,0.03)	0.01 (-0.03,0.05)	0.02 (-0.03,0.06)	0 (-0.02,0.01)
Non-Hispanic blacks	**0.02 (0,0.04)**	**0.02 (0,0.04)**	**0.04 (0.02,0.07)**	0.02 (-0.01,0.04)	0 (-0.01,0.02)
Non-Hispanic Asian Americans	0.01 (-0.02,0.03)	-0.02 (-0.04,0.01)	0.01 (-0.01,0.03)	0.01 (-0.03,0.05)	0.02 (-0.02,0.05)
Non-Hispanic Native Americans	0.21 (-0.03,0.45)	0.05 (-0.17,0.28)	-0.07 (-0.24,0.09)	0.04 (-0.05,0.13)	-0.05 (-0.24,0.15)

https://doi.org/10.1371/journal.pone.0219711.t004

Non-Hispanic Native Americans and Non-Hispanic whites, with the corresponding rates of mortality in Hispanics and Non-Hispanic blacks decreasing for ages 35-44y; for older age groups (ages 55-74y), the largest increase between 2000–2011 was in Hon-Hispanic blacks. For the 2011–2017 period, for persons aged 25-44y, the largest increases in the rates of mortality involving poisoning by narcotics and psychodysleptics were in Non-Hispanic whites, followed by Non-Hispanic Native Americans/Non-Hispanic Blacks; for persons aged over 45y, the largest increases in the rates of mortality involving poisoning by narcotics and psychodysleptics between 2011–2017 were in Non-Hispanic blacks, followed by Non-Hispanic whites, then Non-Hispanic Native Americans. Increases in the rates of mortality involving poisoning by narcotics and psychodysleptics between 2011–2017 were lowest in Non-Hispanic Asians.

Table 6 presents the relative (fold) increases in the average annual rates of mortality for categories B-E in Table 1 in different age groups in the overall population of US adults for the 2015–2017 period vs. 2000–2002 period, as well as for the 2011–2014 period vs. 2000–2002 period. Table 6 shows major increases in mortality involving poisoning, particularly by narcotics and psychodysleptics (especially in persons aged 55-74y), as well as psychotropic medications, particularly for individuals aged 45-64y. Increases in the rates of mortality involving poisoning by both psychotropic medications but not narcotics and psychodysleptics, as well as for sedative-hypnotic medications but not narcotics and psychodysleptics for the 2011–2014 period vs. 2000–2002 period were greater than the corresponding increases in the rates of

Table 5. Annual change in mortality rates involving poisoning by narcotics and psychodysleptics (ICD-10 codes T40.xx present as either underlying or contributing causes of death; category B in Table 1) between 2000–2011 and between 2011–2017 per 100,000 individuals in different age/racial groups.

2000–2011 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**1.24 (1.15,1.34)**	**0.76 (0.59,0.92)**	**1.17 (0.98,1.37)**	**0.78 (0.74,0.83)**	**0.19 (0.17,0.21)**
Hispanics	0.07 (0,0.15)	**-0.28 (-0.38,-0.18)**	0.01 (-0.19,0.21)	**0.33 (0.27,0.4)**	**0.08 (0.03,0.13)**
Non-Hispanic blacks	-0.05 (-0.18,0.08)	**-0.73 (-1.08,-0.37)**	-0.1 (-0.64,0.43)	**1.01 (0.8,1.22)**	**0.23 (0.09,0.37)**
Non-Hispanic Asian Americans	**0.10 (0.06,0.15)**	**0.04 (0,0.08)**	**0.05 (0,0.1)**	**0.08 (0.05,0.11)**	0.01 (-0.02,0.04)
Non-Hispanic Native Americans	**1.11 (0.84,1.39)**	**1.4 (0.85,1.96)**	**1.52 (1.18,1.85)**	**0.94 (0.69,1.2)**	0.21 (-0.13,0.54)
2011–2017 period					
	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
Non-Hispanic whites	**4.34 (3.04,5.65)**	**3.74 (2.62,4.86)**	**2.1 (1.47,2.73)**	**1.79 (1.54,2.04)**	**0.44 (0.4,0.49)**
Hispanics	**1.35 (0.88,1.82)**	**1.24 (0.82,1.66)**	**0.86 (0.39,1.34)**	**0.81 (0.54,1.08)**	**0.40 (0.28,0.52)**
Non-Hispanic blacks	**2.05 (1.22,2.87)**	**2.64 (1.61,3.67)**	**3.39 (1.76,5.03)**	**4.00 (2.53,5.47)**	**2.3 (1.74,2.86)**
Non-Hispanic Asian Americans	**0.46 (0.31,0.6)**	**0.21 (0.05,0.37)**	**0.15 (0.03,0.27)**	0.08 (-0.01,0.16)	0.04 (-0.04,0.12)
Non-Hispanic Native Americans	**2.22 (1.2,3.24)**	**2.14 (0.54,3.74)**	**1.15 (0.25,2.04)**	**0.93 (0.38,1.47)**	0.34 (-0.19,0.88)

https://doi.org/10.1371/journal.pone.0219711.t005

prescribing for those medications, particularly for persons aged 45-64y (Table 6 vs. [31])–see Discussion.

There were no correlations between state-specific rates of mortality involving poisoning by psychotropic drugs but not narcotics/psychodysleptics and state-specific rates of mortality involving poisoning by narcotics/psychodysleptics during the 2013–2017 period, suggesting potential differences in factors behind those two epidemics; those correlations were -0.06 (95%

Table 6. Relative (fold) increases in the rates of mortality involving poisoning by different substances (categories C, D, E, and B in Table 1) for different age groups of US adults for the 2015–2017 period vs. the 2000–2002 period, as well as the 2011–2014 period vs. the 2000–2002 period.

2015–2017 vs. 2000–2002 periods	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
medicaments but not narcotics and psychodysleptics	2.33	2.07	2.56	3.1	1.43
psychotropic drugs but not narcotics and psychodysleptics	3.22	2.75	3.48	5.37	3.94
sedative-hypnotic drugs but not narcotics and psychodysleptics	3.06	1.75	2.27	2.75	1.73
narcotics and psychodysleptics	4.29	2.32	2.62	6.54	6.33
2011–2014 vs. 2000–2002 periods	Ages 25-34y	Ages 35-44y	Ages 45-54y	Ages 55-64y	Ages 65-74y
medicaments but not narcotics and psychodysleptics	1.64	1.48	1.92	2.24	1.27
psychotropic drugs but not narcotics and psychodysleptics	1.95	1.65	2.3	3.24	2.5
sedative-hypnotic drugs but not narcotics and psychodysleptics	2.26	1.47	2	2.31	1.35
narcotics and psychodysleptics	2.42	1.38	1.89	4.14	3.82

https://doi.org/10.1371/journal.pone.0219711.t006

CI (-0.33,0.22)) for persons aged 45-64y, and -0.16(-0.42,0.12) for persons aged 25-44y. Further details on the geographic spread of the two epidemics are presented in the Supporting Information (S1 File).

Discussion

While the rise in mortality by narcotic, including opiate poisoning, particularly during the most recent years in well documented ([5,9]), our understanding of the contribution of medicaments other than narcotics to mortality is more limited. Moreover, there are differences in the rates of consumption of different medications between the different racial groups [10–18], and those differences may reflect differences in the rates of adverse outcomes associated with medication use in different racial groups [19–24,26,27]. In this study, we have shown significant increases in the rates of mortality involving poisoning by medicaments other than narcotics and psychodysleptics in different age/racial groups, both for the 2000–2011 period, and even more so for the 2011–2017 period. Those increases were particularly large in non-elderly Non-Hispanic Native Americans and whites. The majority of deaths involving poisoning by medicaments other than narcotics and psychodysleptics, as well as most of the increases in the corresponding mortality rates were for deaths involving poisoning by psychotropic medications.

Significant increases in prescribing for antidepressants and antipsychotic (as well as sedative-hypnotic) drugs in different age groups of US adults took place during the study period [31]. For example, for the 2011–2014 period, 17.5% of US adults aged 45-64y and 18.7% of those aged 65-74y reported receiving antidepressant medications during the last 30 days, compared to 10.5% and 9.3% correspondingly for the 1999–2002 period. At the same time, relative increases in the rates of mortality involving poisoning by psychotropic medications but not narcotics and psychodysleptics were greater than increases in prescribing for psychotropic medications, particularly for persons aged 45-64y (Table 6 vs. [31]). This means that the likelihood of a poisoning death per unit of prescribing of psychotropic or sedative-hypnotic medications has increased in the overall population of US adults to whom those medications are prescribed, particularly in the 45-64y age group. This doesn't appear to be the case in several other countries (e.g. Australia), where the rates of death per unit of prescribing of antipsychotic medication have decreased somewhat with time [32], which may be related to the shift to less toxic drugs [33,32]. In the UK and the European union, rates of mortality involving poisoning by drugs and medications are notably lower than in the US [34,35]; moreover, in the UK, rates of mortality involving poisoning by both narcotics and antipsychotic drugs have not experienced such major increases as the corresponding rates during the same period in the US [35]. Further work is needed to better understand the types of individuals, as well as the types of drugs/medications (e.g. 1st vs. 2nd generation antipsychotic medications [33,32]) that are associated with fatal outcomes resulting from consumption of those substances. We should note that while rates of prescribing of certain medications such as antidepressants to US adults aged over 75y have increased significantly [31], rates of mortality involving poisoning by medications but not narcotics/psychodysleptics in US adults aged over 75y have decreased with time (results not included), possibly having to do with a shift to less toxic drugs [33]. Comparison of the mortality trends between US adults aged over 75y vs. non-elderly US adults points to the possibility of self-harm being a factor in the increase in the rates of mortality associated with poisoning by medications in non elderly US adults (particularly non-Hispanic whites), which may also be related to the increases in the rates of mortality associated with alcohol poisoning and suicide in those population groups [8].

While rates of mortality involving poisoning by medicaments other than narcotics and psychodysleptics are lower than the rates of mortality involving poisoning by narcotics and psychodysleptics, the pernicious effects that medication use/misuse may have on health, including mortality outcomes are not restricted to deaths that involve poisoning by medicaments listed on a death certificate. Indeed, a number of studies, e.g. [19–24] have suggested elevated risks for mortality and other health-related outcomes associated with the use of psychotropic medications (both antipsychotic medications and antidepressants) and sedative-hypnotic medications (particularly benzodiazepines). Recent work suggests associations between rates of prescribing for penicillins, and rates of mortality and hospitalization for septicemia/sepsis in older adults [26,27]. Additionally, rates of consumption of certain medications, particularly psychotropic drugs, sedative-hypnotic medications and antibiotics in Non-Hispanic whites are higher than in other major racial groups (save for Native Americans) [10–18], and those differences may have an effect on health-related, including mortality outcomes [19–24,26,27]. Our results, as well as other work, e.g. [19–24,26,27] support the need for a comprehensive evaluation of the impact of prescribing/misuse of various medications on health, including mortality outcomes.

Our paper has some limitations. It might be that increases in the rates of mortality involving poisoning by medicaments other than narcotics were affected by changes in notification and coding practices. For example, in light of the increases in the rates of mortality involving poisoning by narcotics/psychodysleptics, a growing fraction of deaths having poisoning by medicaments but not poisoning by narcotics/psychodysleptics on a death certificate could have actually been partly affected by narcotic/psychodysleptic use, with poisoning by narcotics/psychodysleptics not appearing on some of those death certificates. We do not believe that this could largely explain our results as there are no correlations between state-specific rates of mortality involving poisoning by psychotropic drugs but not narcotics/psychodysleptics and state-specific rates of mortality involving poisoning by narcotics/psychodysleptics during the 2013–2017 period (Results; Supporting Information (S1 File)). Additionally, there are notable discrepancies in trends for mortality involving poisoning by narcotics and psychodysleptics vs. mortality involving poisoning by medicaments other than narcotics, particularly for Hispanics and Non-Hispanic blacks, further supporting the notion that deaths involving poisoning by narcotics and psychodysleptics and deaths involving poisoning by medicaments other than narcotics represent different epidemics, and increases in the recorded rates of the latter deaths are not an artifact of the increases in the rates of the former deaths. For example, rates of mortality involving poisoning by medicaments but not narcotics/psychodysleptics in Hispanics aged 35-44y increased between 2000–2011 (Table 2 and Fig 3), while rates of mortality involving poisoning by narcotics and psychodysleptics in that population declined between 2000–2011 (Table 5 and Fig 2); for persons aged 55-64y, increases in mortality involving poisoning by narcotics and psychodysleptics were greater in Non-Hispanic blacks than in Non-Hispanic whites for both the 2000–2011 and the 2011–2017 periods (Table 5), with the opposite being true for increases in mortality involving poisoning by medicaments but not narcotics and psychodysleptics (Table 2). Another possible contributing factor to the increase in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics is change in diagnostic/coding criteria. However, it is unlikely that such changes, if they indeed took place, would be very different for different groups of adults, while growth in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics is notably higher for some age/racial groups compared to others. For example, there were no discernible changes in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics in Non-Hispanic blacks aged 34-54y between 2000–2011 (Table 2), while major changes in the corresponding mortality rates took place in Non-Hispanic whites and

Non-Hispanic Native Americans. Another example is Non-Hispanic whites aged 55-64y vs. Non-Hispanic whites aged 65-74y. In the beginning of the study period, rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics were similar for the two age groups; however, subsequently those rates followed quite different trends for the two age groups (Fig 3). We believe that those differences in trends for different population groups are unlikely to be explained by differences in changes in diagnostic/coding criteria for those population groups, but rather by genuine differences in mortality trends between the different population groups. Finally, we don't know whether increases in prescribing or misuse have contributed to the increases in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics. Significant increases in medication prescribing rates, particularly for antipsychotic and sedative-hypnotic drugs in persons aged 25-44y, and antidepressants in persons aged 45-74y did take place during the study period [31]. At the same time, increases in mortality involving poisoning by psychotropic, as well as sedative-hypnotic drugs, but not narcotics and psychodysleptics were generally greater than increases in prescribing for those medications, particularly for persons aged 45-64y (compare Table 6 to [31]). Additionally, while rates of prescribing of psychotropic medications in individuals aged over 75y increased during the study period [31], rates of mortality involving poisoning by those medications in individuals aged over 75y have decreased, which is unlike the case of younger individuals. All of this suggests the potential role of misuse of the antidepressant/antipsychotic, as well as sedative-hypnotic medications in the increases in the rates of mortality by poisoning in certain population groups, particularly non-elderly white and Native Americans.

We believe that despite some limitations, our study shows significant increases in the rates of mortality involving poisoning by medicaments but not narcotics and psychodysleptics, especially poisoning by psychotropic drugs in different age/racial groups, particularly non-elderly Non-Hispanic Native Americans and whites, both between 2000–2011, and even more so between 2011–2017. Moreover, some of those increases in mortality rates have significantly exceeded the increases in prescription rates for the corresponding medications, pointing to the potential role of medication misuse. Those results, as well as earlier studies showing associations between medication use and health-related and mortality outcomes (e.g. [19–24,26,27]), including for deaths that do not have poisoning listed on a death certificate further support the need for a comprehensive evaluation of the impact of prescribing and misuse of various medications on health and mortality outcomes in different population groups, as well as the related guidance regarding the use of those medications. Additionally, such analyses may help elucidate the role of medication use/misuse in the long-term decline in life expectancy in Non-Hispanic whites compared to other major racial groups in the US [1].

Supporting information

S1 Checklist. STROBE Statement for a cohort study.
(DOC)

S1 File. Supporting Information for "Rise in mortality involving poisoning by medicaments other than narcotics, including poisoning by psychotropic drugs in different age/racial groups in the US".
(DOCX)

Author Contributions

Conceptualization: Edward Goldstein.

Formal analysis: Edward Goldstein.

Investigation: Edward Goldstein.

Methodology: Edward Goldstein.

Software: Edward Goldstein.

Writing – original draft: Edward Goldstein.

Writing – review & editing: Edward Goldstein.

References

1. Xu J, Murphy SL, Kochanek KD, Bastian B, Arias E. Deaths: Final data for 2016. National Vital Statistics Reports 2018; 67(5). Updated on July 26, 2018. Accessed on Dec 1, 2018. Available from: https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_05.pdf PMID: 30248015
2. Heron M, Hyert DL, Murphy SL, Xu J, Kochanek KD, Tejada-Vera B. Deaths: Final data for 2006. National Vital Statistics Reports 2009; 57(14). Updated on Apr 17, 2009. Accessed on Dec 1, 2018. Available from: https://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_14.pdf PMID: 19788058
3. Kochanek KD, Murphy SL, Xu J, Tejada-Vera B. Deaths: Final data for 2014. National Vital Statistics Reports 2016; 65(4). Updated on June 30, 2016. Available from: https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_04.pdf PMID: 27378572
4. Muennig PA, Reynolds M, Fink DS, Zafari Z, Geronimus AT. America's Declining Well-Being, Health, and Life Expectancy: Not Just a White Problem. Am J Public Health. 2018; 108(12):1626–1631 https://doi.org/10.2105/AJPH.2018.304585 PMID: 30252522
5. Dowell D, Noonan RK, Houry D. Underlying factors in drug overdose deaths. JAMA. 2017; 318 (23):2295–2296 https://doi.org/10.1001/jama.2017.15971 PMID: 29049472
6. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and Opioid-Involved Overdose Deaths—United States, 2013–2017. MMWR 2018; 67. Updated on Dec. 21, 2018. Accessed on Dec 27, 2018. Available from: https://www.cdc.gov/mmwr/volumes/67/wr/mm675152e1.htm?s_cid=mm675152e1_w
7. Abraído-Lanza AF, Dohrenwend BP, Ng-Mak DS, Turner JB. The Latino mortality paradox: a test of the "salmon bias" and healthy migrant hypotheses. Am J Public Health. 1999; 89(10):1543–8. https://doi.org/10.2105/ajph.89.10.1543 PMID: 10511837
8. Stein EM, Gennuso KP, Ugboaja DC, Remington PL. The Epidemic of Despair Among White Americans: Trends in the Leading Causes of Premature Death, 1999–2015. Am J Public Health. 2017; 107 (10):1541–1547 https://doi.org/10.2105/AJPH.2017.303941 PMID: 28817333
9. Woolf SH, Chapman DA, Buchanich JM, Bobby KJ, Zimmerman EB, Blackburn SM. Changes in midlife death rates across racial and ethnic groups in the United States: systematic analysis of vital statistics. BMJ. 2018; 362:k3096 https://doi.org/10.1136/bmj.k3096 PMID: 30111554
10. Briesacher B1, Limcangco R, Gaskin D. Racial and Ethnic Disparities in Prescription Coverage and Medication Use. Health Care Financ Rev. 2003; 25(2):63–76 PMID: 15124378
11. Olesen SW, Grad YH. Racial/Ethnic Disparities in Antimicrobial Drug Use, United States, 2014–2015. Emerg. Infec. Diseases 2018; 24(11):2126–2128
12. Gahbauer AM, Gonzales ML, Guglielmo BJ. Patterns of Antibacterial Use and Impact of Age, Race-Ethnicity, and Geographic Region on Antibacterial Use in an Outpatient Medicaid Cohort. Pharmacotherapy. 2014; 34(7):677–85 https://doi.org/10.1002/phar.1425 PMID: 24753176
13. Pierre G, Thorpe RJ Jr, Dinwiddie GY, Gaskin DJ. Are there racial disparities in psychotropic drug use and expenditures in a nationally representative sample of men in the United States? Evidence from the Medical Expenditure Panel Survey. Am J Mens Health. 2014; 8(1):82–90 https://doi.org/10.1177/1557988313496564 PMID: 23884790
14. Pratt LA, Brody DJ, Gu Q. Antidepressant Use Among Persons Aged 12 and Over: United States, 2011–2014. NCHS Data Brief No. 283. 2017 (283):1–8. Updated on Aug 2017. Accessed on Dec 1, 2018. Available from: https://www.cdc.gov/nchs/data/databriefs/db283.pdf
15. González HM, Croghan TW, West BT, Tarraf W, Williams DR, Nesse R, et al. Antidepressant Use among Blacks and Whites in the United States. Psychiatr Serv. 2008; 59(10): 1131–1138. https://doi.org/10.1176/appi.ps.59.10.1131 PMID: 18832498
16. Blazer D, Hybels C, Simonsick E, Hanlon JT. Sedative, hypnotic, and antianxiety medication use in an aging cohort over ten years: a racial comparison. J Am Geriatr Soc. 2000; 48(9):1073–9. https://doi.org/10.1111/j.1532-5415.2000.tb04782.x PMID: 10983906

17. McCabe SE. Correlates of nonmedical use of prescription benzodiazepine anxiolytics: results from a national survey of U.S. college students. Drug Alcohol Depend. 2005; 79(1):53–62. https://doi.org/10.1016/j.drugalcdep.2004.12.006 PMID: 15943944

18. Kaufmann CN, Spira AP, Alexander GC, Rutkow L, Mojtabai R. Trends in prescribing of sedative-hypnotic medications in the United States: 1993–2010. Pharmacoepidemiol Drug Saf. 2016; 25(6):637–45. https://doi.org/10.1002/pds.3951 PMID: 26711081

19. Maslej MM, Bolker BM, Russell MJ, Eaton K, Durisko Z, Hollon SD, et al. The Mortality and Myocardial Effects of Antidepressants Are Moderated by Preexisting Cardiovascular Disease: A Meta-Analysis. Psychother Psychosom. 2017; 86(5):268–282 https://doi.org/10.1159/000477940 PMID: 28903117

20. Honkola J, Hookana E, Malinen S, Kaikkonen KS, Junttila MJ, Isohanni M, et al. Psychotropic medications and the risk of sudden cardiac death during an acute coronary event. Eur Heart J. 2012; 33 (6):745–51 https://doi.org/10.1093/eurheartj/ehr368 PMID: 21920969

21. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death. N Engl J Med. 2009; 360(3):225–35 https://doi.org/10.1056/NEJMoa0806994 PMID: 19144938

22. Baandrup L, Iversen HK, Ibsen R, Kjellberg J. Mortality and use of psychotropic medication in patients with stroke: a population-wide, register-based study. BMJ Open. 2016; 6(3):e010662 https://doi.org/10.1136/bmjopen-2015-010662 PMID: 26956165

23. Baricault B, Palmaro A, Lapeyre-Mestre M. Mortality Related to Benzodiazepines or Other Psychotropic Drugs in Patients with Cancer. Clin. Therapeutics 217; 39(8):e12–e13

24. Johnell K, Jonasdottir Bergman G, Fastbom J, Danielsson B, Borg N, Salmi P. Psychotropic drugs and the risk of fall injuries, hospitalisations and mortality among older adults. Int J Geriatr Psychiatry. 2017; 32(4):414–420 https://doi.org/10.1002/gps.4483 PMID: 27113813

25. Huikuri HV. Psychotropic Medications and the Risk of Sudden Cardiac Death. J Am Heart Assoc. 2015; 4(2):e001894 https://doi.org/10.1161/JAHA.115.001894 PMID: 25713295

26. Goldstein E. Prescribing of different antibiotics, rates of sepsis-related mortality and bacteremia in the US and England, and the utility of antibiotic replacement vs. reduction in prescribing. BioRxiv 2019. Accessed on June 1, 2019. Available from: https://www.biorxiv.org/content/10.1101/527101v4

27. Goldstein E, Olesen SW, Karaca Z, Steiner CA, Viboud C, Lipsitch M. Levels of outpatient prescribing for four major antibiotic classes and rates of septicemia hospitalization in different US states. BioRxiv 2019. Accessed on June 1, 2019. Available from: https://www.biorxiv.org/content/10.1101/404046v2

28. Goldstein E, MacFadden DR, Karaca Z, Steiner CA, Viboud C, Lipsitch M. Antimicrobial resistance prevalence, rates of hospitalization with septicemia and rates of mortality with sepsis in adults in different US states. Int J Antimicrob Agents. 2019; pii: S0924-8579(19)30056-1

29. US CDC Wonder. Multiple Cause of Death, 1999–2017 Request. Updated on Dec. 18, 2018. Accessed on Dec. 21, 2018. Available from: https://wonder.cdc.gov/mcd-icd10.html

30. US CDC Wonder. Underlying cause of death 1999–2017. 2018. Updated on Dec. 6, 2018. Accessed on Feb. 1, 2019. Available from: https://wonder.cdc.gov/wonder/help/ucd.html

31. US CDC. Selected prescription drug classes used in the past 30 days, by sex and age: United States, selected years 1988–1994 through 2011–2014. Health, United States, 2016—Individual Charts and Tables. 2016. Updated on Apr. 9, 2018, Accessed on Dec. 1, 2018. Available from: https://www.cdc.gov/nchs/data/hus/2016/080.pdf

32. Berling I, Buckley NA, Isbister GK. The antipsychotic story: changes in prescriptions and overdose without better safety. Br J Clin Pharmacol. 2016; 82(1):249–54 https://doi.org/10.1111/bcp.12927 PMID: 26945707

33. Buckley NA, Whyte IM, Dawson AH, Isbister GK. A prospective cohort study of trends in self-poisoning, Newcastle, Australia, 1987–2012: plus ça change, plus c'est la même chose. Med J Aust 2015; 202: 438–42. PMID: 25929508

34. UK Office for National Statistics. Deaths related to drug poisoning in England and Wales: 2017 registrations (2018). Accessed on June 1, 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2017registrations

35. European Monitoring Center for Drugs and Drug Addiction. European Drug Report: Trends and Developments 2017 (2017). Accessed on June 1, 2019. Available from: http://www.emcdda.europa.eu/system/files/publications/4541/TDAT17001ENN.pdf