Brief communication

Cause-specific mortality among people previously hospitalized with opioid-related conditions: a retrospective cohort study

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ABSTRACT

Purpose: Although numerous studies have reported on all-cause mortality among opioid users, few have provided estimates for specific causes of death. We report all-cause and cause-specific mortalities for a large cohort of individuals with a history of opioid-related disorders.
Methods: We used administrative data on people discharged from California hospitals between 1990 and 2005 with diagnoses of opioid dependence, abuse, poisoning, or withdrawal. We calculated crude and standardized cause-specific mortality rates and ratios.
Results: Data included 68,066 individuals and 390,438 person-years of follow-up. There were 13,107 deaths (a crude mortality rate of 33.6 per 1000 person-years). The standardized mortality rate was 37.6 per 1000, and the standardized mortality ratio (SMR) was 4.36 (95% confidence interval [CI], 4.30–4.43). Standardized mortality ratios were greater than 1 for all specific causes except Alzheimer's disease, and were the highest for drug-induced deaths (62.2, 95% CI, 58.2–66.1), human immunodeficiency virus (24.6, 95% CI, 22.3–26.9), and endocarditis (23.2, 95% CI, 15.3–31.3). The broad causes associated with the most excess deaths were drug- or alcohol-induced death (23% of excess deaths), cancer (18%), heart disease (14%), and lower respiratory disease (7%).
Conclusions: Mortality in this cohort was very high. Most excess deaths were not directly due to drug use, but many were from causes associated with the use of tobacco or alcohol. Mortality for cancers not linked to tobacco or alcohol was also elevated, suggesting that admission for opioid-related causes serves in part as a risk marker for preexisting disease.

Introduction

Although opioids have limited direct toxicity [1], mortality among people dependent on them is very high. Much of this excess mortality is attributable to overdose, infectious disease, and trauma, but other causes of death have also been shown to be elevated in this population (e.g., [2]). Particularly with increases in recent years in nonmedical use of prescription opioids [3,4], the associated population health burden has become increasingly significant [5]. Much research has focused on overdose, however, with somewhat less attention to other causes of death. Data on other sources of death and ill-health may inform policy approaches and medical interventions concerned with the total burden of disease and disability. Associations with specific causes may also help to identify pathways underlying the association between opioid use

and disease and may also contribute to an evidence base for the improvement of medical assessment of people with opioid-related problems.

The purpose of this study was to examine patterns of cause-specific mortality in a very large cohort of people with a history of inpatient treatment for opioid dependence, abuse, withdrawal, or poisoning. Results on all-cause or broad-category mortalities have been reported for numerous cohorts (58 are reviewed in a study by Degenhardt et al. [2]), most with total samples between 100 and 5000 people. Two large cohorts have reported on cause-specific mortality among people with opioid-related disorders: Bargagli et al. [6] for a Rome-based cohort of 11,432 people, 92% of whom were heroin users; and Degenhardt et al. [7] for 43,789 receiving opioid agonist therapy in Australia. Both reported high all-cause mortality, with significant excess deaths not only for drug overdose but also for most medical causes, as well.

The present study extends previous work in several ways. First, the size of the cohort studied, along with the lengthy follow-up period, makes it possible to obtain high levels of precision and to report on numerous specific causes of death. Second, we report on a

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large North American cohort; most of the studies to date have used data from European countries or Australia. The widespread nonmedical use of prescription analgesics in the United States in the period studied [3,4] may result in a comparatively low proportion of intravenous users [8]. Third, we present results for a much larger number of causes of death and follow Centers for Disease Control and Prevention (CDC) definitions of these causes, which aid comparison with other US populations. Our cohort is also unlike those previously reported in that it is comprised people with a history of inpatient admission with a diagnosis of an opioid-related disorder.

Methods

Data

We obtained data on inpatient admissions from the California Office of Statewide Health Planning and Development (OSHPD). These data include inpatient stays in all licensed general acute, acute psychiatric, chemical dependency, and general psychiatric hospitals in California between 1990 and 2005. Reabstraction studies have reported specificities for diagnoses from 0.98 to 1.00 and sensitivities between 0.88 and 1.00 [9,10]. Mortality data come from the California Vital Statistics Database. These records were linked to inpatient admissions by the OSHPD using a probabilistic approach with reported positive and negative predictive values of 0.994 and 0.998, respectively [11].

We used California in the year 2000 as a reference population, obtaining relevant demographic and mortality data from the Center for Disease Control (Table 1; [12]). These data are publicly available through the CDC Wonder system. Although 2000 is slightly after the midpoint of the study, changes in the treatment of ethnicity in the US census and in CDC reporting of aggregate causes of death in the late 1990s meant that using earlier data would have prevented standardization for Hispanic ethnicity (a group which accounts for a substantial portion of the California population).

Inpatient episodes in California were coded using *International Classification of Diseases* (ICD)-9 diagnoses, whereas deaths were assigned principal causes from ICD-9 for years until 1998 and from ICD-10 thereafter. We recoded all causes of death into categories used by the CDC and other US government bodies in much of their reporting (e.g., [13]). We first applied CDC codings for "alcohol-induced" and "drug-induced" causes of death [14]; these categories include accidental and intentional overdose and medical conditions resulting directly from substance use (e.g., drug-induced polyneuropathy). We then coded remaining deaths into the CDC's set of 113 common causes of death, which includes the most common causes of death in the United States. This approach results in 115 exclusive causes. Finally, we report on broader causes of death produced by combinations of these causes, again using classifications used by the CDC [15].

Permissions for data use were obtained from the OSHPD, whereas ethics approval for the study was received from the Center for Addiction and Mental Health and from the State of California Committee for the Protection of Human Subjects.

Analysis

We selected individuals with at least one inpatient admission during the study period with a diagnosis of opioid dependence, abuse, or withdrawal (ICD-9 codes 304.00, 304.01, 304.02, 304.03, 304.70, 304.71, 304.72, 304.73, 305.50, 305.51, 305.52, and 305.53).

We produced standardized mortality rates using direct standardization, adjusting for age, sex, and race. We used 10-year age strata (15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and

Table 1
Reference population: California, 2000

Age group (y)	Females			Males		
	N	Deaths	Mortality rate*	N	Deaths	Mortality rate*
15–24	2,315,020	740	0.3	2,517,156	2364	0.9
25–34	2,535,262	1148	0.5	2,693,800	3066	1.1
35–44	2,712,847	3295	1.2	2,772,494	5994	2.2
45–54	2,197,874	6145	2.8	2,133,761	10,285	4.8
55–64	1,356,785	9409	6.9	1,257,308	13,487	10.7
65–74	1,033,120	17,973	17.4	854,703	22,276	26.1
75–84	757,189	33,852	44.7	524,989	32,957	62.8
85+	291,475	40,290	138.2	134,182	21,842	162.8
Total	13,199,572	112,852	8.5	12,888,393	112,271	8.7

* Per 1000 person-years.

85+ years) and coded race and ethnicity into four categories: Hispanic of any race, white, black, and other. We used a normal approximation to the Poisson distribution to obtain confidence intervals (CIs) around crude and standardized rates [16]. As our sample includes individuals for whom opioid-related disorder was not the primary diagnosis, we repeated our analysis including only those individuals, as a test of the sensitivity of our results to that decision. We treated age as a static variable, using each individual's age at the midpoint of their time at risk to perform comparisons with the reference population. Finally, we computed years of potential life lost before the age of 75 years [YPLL(75)] because of each cause of death. The analysis was performed using R 2.14 [17] and Microsoft Access 2003 (Microsoft Corporation, Seattle, Washington).

We report all causes of death where the number of deaths was 20 or more and where the relative standard error for the standardized rate did not exceed 25%. Twenty events is a widely recommended minimum number for direct standardization [18], whereas CDC reporting commonly limits relative standard errors to 20%–30% (e.g., [19]).

Results

Cohort and population sizes and demographics are presented in Table 2. Ten people with missing demographic information, representing 70.4 years of follow-up and one death, were excluded from the analysis. We identified 68,066 people with an admission for opioid dependence, abuse, poisoning, or withdrawal during the study period. A total of 390,438 person-years of follow-up were available, an average of 5.7 years per person. There were 13,107 deaths over the study period, corresponding to a crude mortality rate of 33.6 per 1000 person-years. The crude mortality rate for the reference population (California in the year 2000) was 8.6. Deaths in the cohort over the study period represent a total of 250,810 years of potential life lost before the age of 75 years, an average of 16,720 per calendar year.

The standardized mortality rate for the opioid cohort was 37.6 per 1000 (95% CI, 37.0–38.1) and the standardized mortality ratio (SMR) was 4.36 (95% CI, 4.30–4.43). Table 3 presents SMRs for broad causes and for the specific causes with SMRs above 5 that were also responsible for 1% or more of cohort deaths. A complete list of causes is available online as ancillary material. Relative to the reference population, mortality ratios in the study cohort were the highest among young adults, because of very low background rates for these groups (Table 2). Crude mortality ratios were more than 10 for all age- and sex-groups under 45 years and decreased monotonically with age.

The SMR for drug-induced death was 62.2 (95% CI, 58.2–66.1). As the study cohort is included in the reference population, this number is an underestimate of the true ratio for exposed versus