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All-cause mortality among individuals with disorders related to the use of methamphetamine: A comparative cohort study

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ABSTRACT

Background: Understanding the mortality rate of methamphetamine users, especially in relation to other drug users, is a core component of any evaluation of methamphetamine-related harms. Although methamphetamine abuse has had a major impact on United States (US) drug policy and substance-abuse treatment utilization, large-scale cohort studies assessing methamphetamine-related mortality are lacking.

Methods: The current study identified cohorts of individuals hospitalized in California from 1990 to 2005 with ICD-9 diagnoses of methamphetamine- (n = 74,139), alcohol- (n = 582,771), opioid- (n = 67,104), cannabis- (n = 46,548), or cocaine-related disorders (n = 48,927), and these groups were followed for up to 16 years. Age-, sex-, and race-adjusted standardized mortality rates (SMRs) were generated.

Results: The methamphetamine cohort had a higher SMR (4.67, 95% CI 4.53, 4.82) than did users of cocaine (2.96, 95% CI 2.87, 3.05), alcohol (3.83, 95% CI 3.81, 3.85), and cannabis (3.85, 95% CI 3.67, 4.03), but lower than opioid users (5.71, 95% CI 5.60, 5.81).

Conclusions: Our study demonstrates that individuals with methamphetamine-use disorders have a higher mortality risk than those with diagnoses related to cannabis, cocaine, or alcohol, but lower mortality risk than persons with opioid-related disorders. Given the lack of long-term cohort studies of mortality risk among individuals with methamphetamine-related disorders, as well as among those with cocaine- or cannabis-related conditions, the current study provides important information for the assessment of the comparative drug-related burden associated with methamphetamine use.

1. Introduction

The United States (US) has one of the world's largest methamphetamine markets (United Nations Office on Drugs and Crime, 2010), and methamphetamine abuse has had a major impact on US drug policy legislation (e.g., *Combat Methamphetamine Epidemic Act* of 2005; Sununu, 2005), as well as substance-abuse treatment utilization (e.g., approximately one-third of all recent admissions to publicly funded substance-abuse treatment centers in California were primarily due to methamphetamine; United States Department of Health and Human Services and Substance Abuse and Mental Health Data Archive, 2011). Understanding risk of mortality is a core component of any assessment of methamphetamine-related harms (Darke et al., 2007; Nutt et al., 2007), but there are presently no standardized mortality estimates for methamphetamine users in the United States.

In a recent 2009 systematic review (Singleton et al., 2009) of death patterns among problematic users of amphetamine-type stimulants (ATS; a drug group composed primarily of methamphetamine and amphetamine), the Mental Disorders and Illicit Drug Use Expert Group for the Global Burden of Disease project found only 8 cohort studies addressing mortality issues in the past three decades, and all but one were deemed poor quality (with only one Czech study (Lejckova and Mravcik, 2007) providing standard mortality rates (SMRs)). Since publication of this recent systematic review, three other relevant cohort studies from Denmark (Arendt et al., 2010), Taiwan (Kuo et al., 2010) and Sweden (Stenbacka et al., 2010) have provided SMRs for ATS users. However, the currently available cohort studies have a number of important limitations,

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including relatively small sample sizes and low numbers of deaths; factors which undermine the precision of mortality-related estimates. In addition, it is unclear whether the available mortality findings might extend to US settings.

While the standard approach to calculate SMRs involves adjustment by age and sex, this technique may lead to biased estimates for drug-using cohorts if some drug groups are disproportionately (in relation to the general population) composed of racial groups with varying mortality risk. For example, in California, individuals admitted to publicly funded substance-abuse treatment facilities for primary cocaine-related issues are disproportionately African American, while those admitted for methamphetamine-related treatment are primarily Caucasian (Office of Applied Studies, Substance Abuse and Mental Health Services Administration, 2010). African Americans in California have an elevated risk of mortality in comparison to the general population (Palaniappan et al., 2004) and, as a result, SMRs for treatment-seeking cohorts which do not account for race will yield overestimates for cocaine users, as well as potentially biased estimates for other substance-abuse cohorts.

To address the above concerns in the field, we constructed a study incorporating (1) a large sample of all patients hospitalized in California with methamphetamine use disorders ($n = 74{,}139$), (2) a lengthy follow-up of up to 16 years, (3) a large number of deaths in the methamphetamine cohort ($n = 4122$), (4) standardization of mortality rates not only by age and sex but also by race, a variable capturing significant mortality differences among races in California (Palaniappan et al., 2004), and (5) a descriptive comparison of SMRs of methamphetamine users versus other drug groups.

2. Methods

2.1. Data sources: California Patient Discharge Database (PDD) and Vital Statistics Database (VSD): 1990–2005

The current study, approved by the Research Ethics Board at the Centre for Addiction and Mental Health (CAMH) and the State of California Committee for the Protection of Human Subjects, utilized California Office of Statewide Health Planning and Development (OSHPD) inpatient hospital admission data from January 1, 1990 until December 31, 2005 from the Patient Discharge Database (PDD). The dataset consists of a record containing demographic information and up to 25 diagnoses, based on the International Classification of Diseases, 9th edition (ICD-9), for each inpatient discharged from a California licensed hospital. Licensed hospitals include general acute care, acute psychiatric care, chemical dependency recovery, and psychiatric health facilities. Inpatient data are screened by an automated data-entry and reporting system (MIRCal; California Office of Statewide Health Planning and Development, 2010) and data fields with error rates of 0.1% or higher are returned to the hospitals for correction (Zach, 1990; California Office of Statewide Health Planning and Development, 1995). Reabstraction studies comparing California Office of Statewide Health Planning and Development inpatient data files with original medical records found specificities for diagnoses ranging from 0.98 to 1.00, and sensitivities for diagnoses ranging from 0.88 to 1.00 (California Office of Statewide Health Planning and Development, 1990, 1996).

2.2. Measurement of outcome: mortality

Death records from the California Vital Statistics Database (VSD; which captures all death records for the state) were linked to the Patient Discharge Database inpatient data. The probabilistic matching algorithm linking California inpatient records to state death records has a linkage sensitivity and specificity of 0.9524 and 0.9998, respectively, and positive and negative predictive values of 0.994 and 0.998 (Zingmond et al., 2004).

2.3. Patient group assignment

2.3.1. Methamphetamine group assignment. Individuals aged 15–84 years old were assigned to the methamphetamine group only if they had: (1) an ICD-9 diagnosis, in any diagnostic position, of 304.4 (amphetamine and other psychostimulant dependence), 305.7 (amphetamine or related acting sympathomimetic abuse), 969.7 (psychostimulant poisoning) or E854.2 (accidental (unintentional) psychostimulant poisoning); (2) no ICD-9 indication of any alcohol or drug use other than methamphetamine (using ICD-9 codes identifying the other drug cohorts found in Table 2); and (3) no ICD-9 indication of other drug-use disorders (sedative, hypnotic or anxiolytic dependence: 304.1; hallucinogen dependence: 304.5; other specified drug dependence: 304.6; combination of opioid-type drugs with any other: 304.7; combination of drug-dependence excluding opioid-type drugs: 304.8; unspecified drug dependence: 304.9; hallucinogen abuse: 305.3; sedative, hypnotic or anxiolytic abuse: 305.4; other, mixed, or unspecified drug use: 305.9).

Although the ICD-9 coding framework does not distinguish between methamphetamine and other ATS, it is likely that the ICD-9 amphetamine-related codes serve as reasonable proxies for methamphetamine-related conditions. From 1992 to 2005, there were 514,625 primary amphetamine-related inpatient and outpatient treatment admissions to publicly funded substance abuse treatment programs in California, and methamphetamine accounted for 97.8% of all of these primary amphetamine-related episodes (United States Department of Health and Human Services and Substance Abuse and Mental Health Data Archive, 2011). Also, in California, Arizona, and Nevada, U.S. methamphetamine-precursor legislation, which was designed to reduce the manufacture and supply of methamphetamine, was associated with statistically significant reductions in inpatient hospital admissions with the same ICD-9 amphetamine-related codes as used in our study (Cunningham and Liu, 2003).

2.3.2. Alcohol and other drug groups. Individuals aged 15–84 years old were assigned to only one of the following drug cohorts: cocaine, opioid, cannabis, or alcohol. To be assigned to a drug cohort, an individual must have had: (1) an ICD-9 diagnosis, in any of the diagnoses (up to 25) recorded in the patient's medical record, indicating a condition within only one single drug category (in Table 2), at index admission; (2) no indication in medical records of any alcohol- or drug-use diagnoses outside of their assigned drug cohort as listed in Table 2; and (3) no ICD-9 indication of any other drug use disorders (304.1, 304.5, 304.6, 304.7, 304.8, 304.9, 305.3, 305.4, and 305.9), defined above.

Thus, the algorithm excluded individuals from a drug group who had any ICD-9 diagnostic codes within a medical record or across records indicative of drug use other than that designated by their drug group membership. For example, individuals assigned to the cocaine group could only have cocaine-related ICD-9 diagnostic codes in any of their inpatient records from the time of their first discharge event up until the time of death (or the study end date).

2.4. Analytic plan

2.4.1. Standardized mortality rates. Age-, sex-, and race-adjusted SMRs for all-cause mortality in the alcohol and drug cohorts were calculated with the indirect method (Breslow and Day, 1987), using as reference the 2000 California mortality data from the Center for Disease Control WONDER System (a publicly available database of mortality information by the Centers for Disease Control and Prevention, 2010).

We chose the year 2000 as the reference year for our calculation of the cohort-specific SMRs for a number of reasons: (1) the year 2000 was a census year in the United States, and the population estimates for California would be more exact than census-interim-year estimates; (2) the year 2000 represented an approximate halfway point during the 16-year study; (3) our population-level mortality statistics were taken from the CDC WONDER system, and this system only began to record detailed race/ethnicity information beginning in 1999 (Hispanic ethnicity information began in this system in 1999); given the large proportion of Hispanic individuals in California and the important mortality variation across racial/ethnic groups in California, we decided to use the census year closest to the initiation of this detailed race/ethnicity data collection in the WONDER system.

To calculate the observed number of deaths in the drug and alcohol cohorts across all years during the span of the study (1990–2005), individuals were placed into the same age cohorts as those defined by the WONDER System based on an individual's age at death; or for censored individuals (i.e., drug users surviving until the end of the study period), an individual's age at the middle point of his/her follow-up time. Person-years of follow-up for each individual admitted during the study span (1990–2005) were calculated as the time from index admission until death or the end of the study (December 31, 2005), whichever came first. Ninety-five percent confidence intervals were calculated assuming the rates followed a Poisson distribution (Ulm, 1990).

3. Results

Table 1 provides descriptive statistics for demographic information and average follow-up time across each of the cohorts. We found that the methamphetamine cohort had a higher SMR (4.67, 95% CI 4.53, 4.82) than the cocaine (2.96, 95% CI 2.87, 3.05), cannabis (3.85, 95% CI 2.67, 4.03), and alcohol (3.83, 95% CI 3.81, 3.85) cohorts, but a lower SMR than the opioid cohort (5.71, 95% CI 5.60, 5.81) (see Table 2). Also, SMRs within cohorts showed important gender differences, with females having higher SMRs in the alcohol, opioid, and cocaine cohorts, and men having higher SMRs in the methamphetamine and cannabis cohorts.

Table 1
Characteristics of individuals assigned to methamphetamine and other drug cohorts.

		Mean age		Race								Sex (F)		Average follow-up time[a]	
				Black		White		Hispanic		Other					
Cohort	Sample size (*n*)	Years	*sd*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	Years	*sd*
Meth	74,139	31.99	10.31	4.28	3169	67.57	50,072	21.57	15,983	6.59	4884	54.74	40,565	8.46	4.49
Cocaine	48,927	36.18	10.48	49.91	24,414	30.35	14,844	15.41	7538	4.33	2117	46.03	22,514	10.69	4.59
Alcohol	582,771	50.77	15.90	9.00	51,609	66.71	382,759	19.06	109,350	5.23	30,017	27.71	158,992	9.86	4.63
Opioids	67,104	43.03	14.51	10.26	6835	63.03	41,986	21.68	14,440	5.03	3348	49.34	32,890	8.92	4.49
Cannabis	46,548	29.28	12.08	21.55	10,029	57.68	26,846	15.25	7097	5.53	2573	54.24	25,245	7.40	4.00

[a] Mean time (years) from index admission until December 31, 2005; Total person-years of follow-up can be calculated as: sample size × average follow-up time.

4. Discussion

In a recent systematic review of mortality among problematic amphetamine users, Singleton et al. (2009) emphasized the need for long-term cohort studies assessing standardized mortality of ATS users. We addressed this literature deficiency by undertaking a large-scale inpatient cohort study of individuals with methamphetamine-use disorders (74,139 subjects; 4122 deaths), and found that hospitalized methamphetamine users have an approximately five-fold risk of mortality when compared with that of the general population.

Our SMR for methamphetamine users (4.67) is similar to those reported in the three other inpatient or treatment-based studies in which smaller numbers of deaths were observed in the ATS cohorts (Czech: SMR 6.22, 95% CI 4.59, 8.25, 48 deaths (Lejckova and Mravcik, 2007); Danish: SMR 6.0, 95% CI 4.2, 8.3, 33 deaths (Arendt et al., 2010); Taiwanese: SMR 6.02, 95% CI 4.98, 7.06, 130 deaths (Kuo et al., 2010)), but slightly more than the study drawing upon a community-based sample of amphetamine users (Sweden: SMR 3.5, 95% CI 3.1, 3.9, 267 deaths (Stenbacka et al., 2010)). The Czech, Danish, and Swedish investigations provided SMR comparisons for some other commonly used illicit drugs, and these studies found, as observed in our study, a higher mortality for users of opioids/heroin than for ATS.

While a large body of research has examined mortality patterns of opioid users (Degenhardt et al., 2011a), a substantially fewer number of studies have produced standardized mortality estimates for cohorts defined by more common illicit drug use, such as cannabis consumption (Calabria et al., 2010). For example, a recent systematic review of the adverse effects of cannabis found only two cohort studies which provided estimates of all-cause mortality among cannabis users, and this review emphasized the need for more long-term cohort studies to provide SMR-related data (Calabria et al., 2010). Our study of hospitalized patients found a heightened SMR (only somewhat lower than the methamphetamine cohort) for our cannabis group (3.85, 95% CI 3.67, 4.03) – a pattern similar to the only two other available cohort studies providing SMRs (Danish: 4.9, 95% CI 4.2, 5.8 (Arendt et al., 2010); Swedish: 7.4, 95% CI 3.2–14.0 and 8.0, 95% CI 3.5, 15.1 (Stenbacka et al., 2010)). However, it must be recognized that the cannabis users of both studies were limited to a subgroup of users who experienced side effects sufficiently severe to receive a hospital diagnosis or treatment for the drug abuse condition. The explanation for the elevated SMR in the cannabis cohort is unknown, but might possibly be influenced by relatively increased prevalence of comorbid psychiatric or somatic conditions. In this regard, the prevalence of mood and schizophrenia-related disorders was higher in the cannabis cohort vs. that in the other drug groups (data

Table 2
Crude and standardized mortality rates in the methamphetamine and other drug cohorts in California, 1990–2005.

Crude mortality rates

			Deaths per 1000 person-years [95% CI]								
Cohort	Sample size (*n*)	Total deaths	Males	Lower CI	Upper CI	Females	Lower CI	Upper CI	Total	Lower CI	Upper CI
Meth[a]	74,139	4122	**13.92**	13.40	14.44	**5.38**	5.09	5.66	**9.05**	8.78	9.33
Alcohol[b]	582,771	166,482	**51.15**	50.87	51.43	**42.58**	42.18	42.99	**48.69**	48.46	48.93
Cocaine[c]	48,927	4329	**14.65**	14.12	15.18	**7.13**	6.75	7.50	**10.94**	10.62	11.27
Opioid[d]	67,104	12,196	**34.65**	34.39	34.91	**28.75**	28.00	29.51	**31.68**	31.12	32.24
Cannabis[e]	46,548	1806	**12.86**	12.15	13.56	**3.63**	3.32	3.95	**7.42**	7.08	7.76

Standardized mortality rates (SMRs)

			SMRs [95% CI]								
Cohort	*n*	Total deaths	Males[f]	Lower CI	Upper CI	Females[f]	Lower CI	Upper CI	Total[g]	Lower CI	Upper CI
Meth	74,139	4122	**4.85**	4.67	5.04	**4.36**	4.14	4.60	**4.67**	4.53	4.82
Alcohol	582,771	166,482	**3.73**	3.71	3.75	**4.16**	4.12	4.20	**3.83**	3.81	3.85
Cocaine	48,927	4329	**2.81**	2.71	2.91	**3.34**	3.17	3.52	**2.96**	2.87	3.05
Opioid	67,104	12,196	**5.50**	5.36	5.63	**5.98**	5.82	6.14	**5.71**	5.60	5.81
Cannabis	46,548	1806	**4.12**	3.90	4.35	**3.30**	3.03	3.60	**3.85**	3.67	4.03

Abbreviations: Meth, methamphetamine; SMR, standard mortality rates.
[a] ICD codes used to identify methamphetamine cohort: 304.4, 305.7, 969.7 or E854.2.
[b] ICD codes used to identify alcohol cohort: 303, 305.0, or 980.0.
[c] ICD codes used to identify cocaine cohort: 304.2, 305.6, or 985.5.
[d] ICD codes used to identify opioid cohort: 304.0, 305.5, or 965.0.
[e] ICD codes used to identify cannabis cohort: 304.3, or 305.2.
[f] Age- and race-adjusted, as compared to the 2000 California population.
[g] Age-, race-, and sex-adjusted, as compared to the 2000 California population.

not shown). It is also possible that the elevated marijuana-related SMR might be affected by a subgroup within the cohort who present to inpatient hospital primarily with high mortality-risk conditions, such as cancer or HIV/AIDS, along with heavy, palliative use of marijuana.

A 2011 systematic review of cohort studies examining mortality among cocaine users (Degenhardt et al., 2011b) found only four studies (none from the United States) providing cocaine-cohort SMR point estimates spanning from approximately 4–8 – a range slightly higher than found in our study. Whereas the Danish group (Arendt et al., 2010) reported similar SMRs for amphetamine and the related dopaminergic stimulant cocaine, in our larger-sample investigation we found higher mortality estimates for the methamphetamine group than those for cocaine, an observation possibly related to different pharmacokinetic properties of the two stimulants or other lifestyle factors associated with drug use.

Our study found that individuals hospitalized with alcohol-related disorders had a mortality rate nearly 4 times higher than population-proxy controls. This pattern is consistent with prior studies demonstrating SMRs ranging from approximately 2.5–10 among persons admitted to hospital or addictions-treatment facilities with alcohol dependence/abuse problems (e.g., Finney and Moos, 1991; Moos et al., 1994; Campos et al., 2011).

Our study showed important gender differences in mortality rates across the cohorts. Even though males had higher crude mortality rates across all cohorts (see Table 2), women had higher SMRs than men in the alcohol, cocaine, and opioid cohorts. A large body of studies on mortality among illicit drug users has shown that women drug users generally have higher SMRs than do their male counterparts (Darke et al., 2007). This might be explained by two factors: female drug users may engage in relatively higher levels of risk behavior (in comparison to general-population female cohorts) than male drug users vis-a-vis males in the general population; and/or the lower population base rate for mortality among females may elevate the female drug-cohort SMRs across the cohorts. Given prior research suggesting the prominence of methamphetamine use among gay men in California, the elevated male SMR in the methamphetamine group may be due to increased HIV-risk behavior and elevated HIV-related mortality situated in this subpopulation (Halkitis et al., 2001; Shoptaw, 2006; Rudy et al., 2009).

Limitations of our investigation include generic uncertainty regarding accuracy and specificity of the diagnostic codes. Although we can provide no information on amount or pattern of drug use, it is highly likely that the subjects of our study were moderate to high dose and frequent drug users as they had received a hospital diagnosis of a drug abuse condition. In this regard, implications of our epidemiological findings are limited to this subgroup of drug users. In addition, while the criteria for drug cohort assignment eliminated individuals with indication of multiple drug use (sufficient to warrant hospital diagnoses), it is possible that undetected polydrug use occurred within the alcohol and drug cohorts. Also, we did not construct a polydrug cohort because of the differences in accounting for the potential heterogeneity within such a group, especially given the prominent variation in route of administration (e.g., oral versus injection across cohorts) across polydrug clustering. As a result, we felt that use of "single-drug" groups would allow for greater rigor in the interpretation of the SMRs estimates across cohorts.

While our Discussion integrated the findings of the current study into the available research, it is important to note that direct comparisons, within and across studies, of SMRs derived from the indirect approach are subject to a number of important potential confounds, such as differing compositions of the standardization strata variables (e.g., sex, age, and race) in cohorts and reference populations, variations in drug-use practices (e.g., injecting versus smoking) across drug cohorts and study settings, variations in other lifestyle factors associated with specific drug cohorts, and differing patterns of primary diagnosis or reasons for treatment admission across cohorts and studies (Breslow and Day, 1987). In addition, our SMR estimates may be biased due to loss to follow-up; however, this bias is likely to be limited in its effect, as the State of California had one of the lowest national rates of state outmigration during the span of the study (Franklin, 2003).

Our US-based study demonstrates that individuals with methamphetamine-use disorders have a higher mortality risk than those with diagnoses related to other drug use, except opioids. Given that an understanding of mortality risk for methamphetamine users forms an essential component of any evaluation of methamphetamine-related harms, our study provides important information for the assessment of the comparative drug-related burden of methamphetamine use. In addition, our findings highlight the need to develop and implement interventions for this patient population in order to reduce mortality risk, such as needle exchange programs, and education about mortality risk, especially drug overdose (Darke et al., 2007).

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Contributors

All five authors have made substantial contributions to the conception and design of the research, and drafting and critically revising the article. R.C.C., conceived of the study, supervised the statistical analyses, and prepared and critically revised manuscript; J.K.C., contributed to the research design, preparation and critical revision of the manuscript; M.V. contributed to the preparation and critical revision of the manuscript; J.S., contributed to the research design, completed the statistical analyses, and helped to prepare and critically revise the manuscript; S.R.J. contributed to the preparation and critical revision of the manuscript; S.J.K., contributed to the research design, and preparation and revision of the manuscript. All authors gave final approval for submission of the manuscript. Dr. Russ Callaghan (the lead author) had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analyses.

Conflict of interest

None of the authors has a conflict of interest vis-à-vis this manuscript.

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