Risk of Mortality during Four Years after Substance Detoxification in Urban Adults

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ABSTRACT *The objective of this analysis was to assess the mortality rate and risk factors in adults, with substance dependence, who are not receiving primary medical care (PC). Date and cause of death were identified using the National Death Index data and death certificates for 470 adults without PC over a period of almost 4 years after detailed clinical assessment after detoxification. Factors associated with risk of mortality were determined using stepwise Cox proportional hazards models. Subjects were 76% male, 47% homeless, and 47% with chronic medical illness; 40% reported alcohol, 27% heroin, and 33% cocaine as substance of choice. Median age was 35. During a period of up to 4 years, 27 (6%) subjects died. Median age at death was 39. Causes included: poisoning by any substance (40.9% of deaths), trauma (13%), cardiovascular disease (13.6%), and exposure to cold (9.1%). The age adjusted mortality rate was 4.4 times that of the general population in the same city. Among these individuals without PC in a detoxification unit, risk factors associated with death were the following: drug of choice [heroin: hazard ratio (HR) 6.9 (95% confidence interval (CI) 1.6–31.1); alcohol: HR 3.7 (95% CI 0.79–16.9) compared to cocaine]; past suicide attempt (HR 2.1, 95% CI 0.96–4.5); persistent homelessness (HR 2.4, 95% CI 1.1–5.3); and history of any chronic medical illness (HR 2.1, 95% CI 0.93–4.7). Receipt of primary care was not significantly associated with death (HR 0.85, 95% CI 0.34–2.1). Risk of mortality is high in patients with addictions and risk factors identifiable when these patients seek help from the health care system (i.e., for detoxification) may help identify those at highest risk for whom interventions could be targeted.*

KEYWORDS *Alcoholism and addictive behavior, Drug abuse, Substance abuse, Primary care, Mortality*

INTRODUCTION

Addictive disorders are common in the United States at 3.8% for alcohol and 0.6% for drug dependence.¹ Many more people use alcohol and other drugs at levels that place them at risk for consequences.² A sizeable number of deaths in the United

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States are caused by alcohol (85,000) and illicit drugs (17,000) each year (4.2% of all deaths).³ Alcohol and drug dependence increase the risk of death substantially.⁴⁻⁸

As in the general population, death in adults with substance dependence is more common in men than in women.⁹⁻¹¹ Similarly, older age is also associated with mortality in this population.^{10,12,13} But in younger persons, there may also be high risk of death, particularly among blacks and urban residents.^{9,14} Finally, racial and ethnic minorities with substance dependence are at higher risk of death than majority populations with these illnesses.^{9,15,16}

Much of the mortality research including people with substance dependence has focused on injection drug users, primarily of heroin.^{15,17,18} This is likely because of the high prevalence of overdose, among other serious medical consequences, and the concomitant risk of death.⁴ More than two-thirds of illicit drug users in an Australian study reported nonfatal drug overdose in their lifetime,¹⁷ and a substantial proportion of the excess mortality in drug users is because of drug overdose.⁴

In addition to direct pharmacologic consequences, social factors may contribute to excess mortality. For example, homelessness is associated with death among substance users.^{19,20} More than half of all deaths in homeless persons in Atlanta were because of substance use.²¹ The well-known common psychiatric comorbidities of homelessness are not the only explanation for increased mortality in this population. In fact, Hibbs et al. found that homeless persons with substance dependence and no other mental health problems were four times more likely to die than those with mental health problems and no substance dependence. Homeless persons with mental health problems and no substance dependence were three times more likely to die than the general population.²⁰

As might be expected, numerous studies have identified medical illness as a predictor of death in people with substance dependence.^{13,22,23} HIV, chronic liver disease, cardiovascular, infectious, digestive, respiratory, endocrine, metabolic, and hematological disorders contribute to these deaths.^{19,23}

A better understanding of predictors of death among substance-dependent persons may provide information that could help decrease the risk of mortality. Furthermore, studying those without primary medical care (common among people with substance dependence) may select for people, at particularly high risk for death, who are amenable to preventive interventions. Among people with substance dependence, barriers to receipt of care may eclipse need, leading to inadequate care and preventable illnesses. It may be particularly useful to understand these predictors among such persons without primary medical care who are willing to seek help from the health care system (i.e., via detoxification), a point at which intervention has the potential to prevent further morbidity and mortality. The main objectives of this study were to (1) describe the mortality rate and causes of death in alcohol and drug-dependent adults (without primary medical care) after detoxification and (2) identify clinical predictors of mortality that can be recognized at the time of detoxification.

METHODS

Design

The Health Evaluation and Linkage to Primary care (HELP) study was a randomized controlled trial (RCT) testing the effectiveness of a multidisciplinary health assessment and referral to link alcohol and other drug-dependent individuals

to primary care. A detailed description of the HELP study RCT was previously reported.²⁴ After providing written informed consent, eligible subjects were enrolled in the RCT. In the current study, we considered risk of mortality in the prospective follow-up of this cohort. As part of the RCT, subjects provided information regarding substance use, demographic, social, and health status and were sought for follow-up interviews every 6 months for 2 years. The Institutional Review Board at Boston University Medical Center approved the study. Additional privacy protection was secured by the issuance of a Certificate of Confidentiality by the U.S. Department of Health and Human Services.

Subjects

Enrollment occurred between February 1, 1997 and April 1, 1999. Eligible subjects were adult inpatients at a single urban residential detoxification unit, who spoke Spanish or English, reported alcohol, heroin, or cocaine as their first or second drug of choice, and resided in proximity to the primary care clinic to which they would be referred or were homeless. Patients with primary care physicians whom they had seen within the prior 2 years; significant dementia; plans to leave the Boston area that would prevent research participation; failure to provide contact information for tracking purposes; or pregnancy were excluded. Of 642 eligible subjects, 470 (73%) consented to participate and were enrolled.

Data Collection Procedures

Trained research associates administered standard interviews to subjects at study entry (baseline) and follow-up interviews. The Spanish interview instrument used the standardized Spanish versions of scales when available. The remainder of the Spanish questionnaire was translated from the English version, back translated, checked for accuracy, and then corrected.

Independent Variables

Independent variables of interest were all assessed by interview at study entry. They included: age, gender, health literacy [Rapid Estimate of Adult Literacy in Medicine (REALM) score²⁵], first language [English (yes/no)], level of education [high school graduate (yes/no)], suicide attempt (ever), drug or alcohol overdose requiring emergency department attention (ever), drug of choice (alcohol, heroin, or cocaine), addiction severity [Addiction Severity Index (ASI) alcohol and drug scales²⁶], alcohol or drug problems [Inventory of Drug Use Consequences (InDUC-2R)²⁷], physical and mental health-related quality of life [the physical and mental component summary scores (PCS and MCS, respectively) derived from the Short Form Health Survey (SF-36)^{28,29}], depressive symptoms [Center for Epidemiologic Studies Depression (CES-D) scale score³⁰], physician diagnosed chronic medical conditions,³¹ tobacco use in the past 30 days before study entry, and the following in the past 6 months before study entry: health insurance (receipt of Medicaid, Medicare, health insurance from a job or family member's job, or any other health benefits plan that paid for medical care expenses), injection drug use, past physical or sexual abuse,³² buying or selling of sex, any homelessness (one or more nights in a shelter or on the street), and persistent homelessness (>21 days in a shelter or on the street). Receipt of primary care (yes/no) since the last research interview was assessed by a series of detailed questions and was entered as a time-varying covariate.³³

TABLE 1 Baseline characteristics of residential detoxification patients (N = 470) and associated risk for death in bivariable analyses

Characteristic	Frequency	Unadjusted hazard ratio (95% CI)
Median age (Range)	35 (18–60)	1.03 (0.98–1.1)
Male (%)	76	2.5 (0.76–8.4)
Race (%)		
Black	46	1.0
White	37	2.6 (0.98–6.96)
Hispanic	11	4.8 (1.6–14.96)**
Other	6	4.1 (1.0–16.3)*
Uninsured (%)	60	1.3 (0.58–2.9)
Any homelessness (past 6 months) (%)	47	1.4 (0.68–3.1)
Persistent homelessness (≥21 nights past 6 months) (%)	24	2.7 (1.3–5.7)*
Suicide attempt (lifetime) (%)	22	2.6 (1.2–5.5)*
Drug overdose (lifetime) (%)	31	2.5 (1.2–5.4)*
Tobacco (past 30 days) (%)	86	0.63 (0.24–1.7)
Chronic medical illness ^a (%)	47	2.3 (1.0–5.2)*
Drug of choice (%)		
Cocaine	33	1.0
Alcohol	40	5.7 (1.3–25.4)*
Heroin	27	7.7 (1.7–34.4)**
First language (not English) (%)	11	2.0 (0.75–5.3)
Education (high school graduate) (%)	69	1.5 (0.62–3.8)
Injection drug use (past 6 months) (%)	22	2.1 (0.95–4.5)
Physical or sexual abuse (past 6 months) (%)	37	0.91 (0.41–2.1)
Buying or selling sex (past 6 months) (%)	28	0.32 (0.10–1.1)
Health literacy (REALM ^b) median (range)	61 (0–66)	1.0 (0.97–1.0)
Alcohol severity (ASI ^c) median (range)	0.51 (0.00–1.03)	2.3 (0.72–7.2)
Drug severity (ASI ^c) median (range)	0.29 (0.00–0.58)	0.27 (0.02–3.1)
Physical health (PCS ^d) median (range)	48.89 (14.07–74.81)	0.97 (0.93–0.998)*
Mental health (MCS ^e) median (range)	28.56 (6.76–62.18)	0.98 (0.95–1.0)
Depressive symptoms (CES-D ^f) median (range)	34 (1–60)	1.0 (0.99–1.1)

^aOf the subjects, 72% reported undergoing HIV testing; of those, 2.6% reported receipt of positive results.

^bRapid Estimate of Adult Literacy in Medicine

^cAddiction Severity Index

^dSF-36 Physical Component Summary

^eSF-36 Mental Component Summary

^fCenter for Epidemiologic Studies-Depression Scale

**P* < 0.05

***P* < 0.01

Outcome

The primary outcome was time between study entry and death. Deaths and dates of death were identified using either the National Death Index (NDI) (dates of death for NDI come from death certificates),^{34,35} which was provided under an agreement between Boston Medical Center and the Department of Health and Human Services, or reports from family or friends of study subjects. At the end of the study, we searched for all subjects in the NDI during the calendar years 1997–2001. The NDI matches subjects to death records based on 12 identifying criteria (day of birth,

month of birth, year of birth, social security number, first, middle, and last name, sex, race, marital status, state of birth, and state of residence). An algorithm considering the correspondence and weight of each identifying criterion is then used to classify the quality of the matches. We accepted only those matches that fit NDI-recommended quality guidelines. NDI characterized deaths by cause, which was identified by International Classification of Diseases (ICD) ninth edition codes from death certificates.

The survival time was defined as the duration of time between date of study entry and date of death (for those who died). The observation time for those who did not die was defined as the time between date of study entry and December 31, 2001, the end of the NDI search period. The Kaplan–Meier estimator was used to determine the survival probability across the mortality data collection period.

City of Boston mortality rate data for years 1997–2001 were provided by the Boston Public Health Commission. We used this data as a descriptive comparison for the rate observed in study subjects.

Analysis

All analyses used SAS/STAT software, Version 8.2.³⁶ All study subjects were eligible for analysis. Descriptive statistics were used to characterize the study subjects. Age-adjusted mortality rates were estimated for both the study sample and the general population of Boston. The age adjustment was performed using the method of direct standardization, and the United States year 2000 population was used as the standard for the age adjustment. For the purpose of comparison, the mortality rates for the current study sample and the city of Boston (calculated for the years 1997–2001) were annualized to represent a 1-year mortality rate.

Given the small number of events, it was not feasible to fit multivariable Cox regression models containing many predictors. Thus, we used an iterative process to select variables for entry into a stepwise model. Preliminary unadjusted Cox proportional hazards models were used to assess the bivariable associations between each of the 22 independent variables and time until death. Factors that were significant at an alpha level of 0.05 were selected as candidate variables for a stepwise procedure, with the exception of demographic characteristics (age, gender, and race), which were considered potential confounders, and thus, were not included in the stepwise model. The stepwise entry and removal criteria were set at a *P* value of 0.15. Correlations between independent variables were obtained, and no pair of variables had a correlation greater than 0.40. To assess potential confounding because of static demographic characteristics, we fit an additional model that included age, gender, and race with the statistically significant variables identified by the stepwise procedure. Reported *P* values are two-tailed, and a *P* value of less than 0.05 was considered statistically significant.

RESULTS

Subject Characteristics (N = 470)

Subject characteristics appear in Table 1. Of the 470 subjects, 2 died before their 6-month interview, and 400 of 468 (85%) completed at least one follow-up research interview; of these, 253 (63%) reported receipt of at least 1 primary care visit.

TABLE 2 Risk factors for death in adults with addictions in multivariable analysis*

Outcome	Hazard ratio (95% CI)	P value
Drug of choice		
Heroin vs. cocaine	6.9 (1.6–31.1)	0.01
Alcohol vs. cocaine	3.7 (0.78–16.9)	0.09
Persistent homelessness (≥ 21 nights in past 6 months)	2.4 (1.1–5.3)	0.03
Suicide attempt (ever)	2.1 (0.96–4.5)	0.06
Chronic medical illness	2.1 (0.93–4.7)	0.07

*Analysis based on a stepwise Cox regression model (entry and removal criteria was set at a *P* value of 0.15) that considered the variables listed in the table and drug overdose ever

Mortality and Causes of Death

The 470 subjects were observed for a median (range) of 46 (1–56) months and 1,728 person-years; of the 470 subjects, 27 (6%) died between 1997 and 2001. The probability of death by 12, 24, and 36 months was 1.7, 3.4, and 5.1%, respectively. The median age at death was 39. Twenty-four (89%) deaths were identified using NDI data, and the remainder was identified in reports from families or friends. Cause of death data was available for 22 (82%) of the deaths. Of these 22 deaths, the most common cause of death was poisoning (41%). Of the nine deaths caused by poisoning, seven were attributed to narcotics, one to analgesics, and one was unspecified. Trauma (one each of homicide, motor vehicle crash, and pedestrian motor vehicle crash) and cardiovascular disease were each causes for three (14%) of the deaths. Exposure to cold and alcohol abuse were each the cause of two (9%) deaths. Diabetes, malignant neoplasm of lung, and intracerebral hemorrhage each caused one (5%) death.

The age adjusted mortality rate for the study cohort was estimated as 1,608 per 100,000 people, 4.4 times that of the general population in the City of Boston (368 per 100,000 people).

Predictors of Risk of Death

In unadjusted bivariable analyses of static demographic characteristics, race was associated with higher risk of mortality. The risk of death was higher for those who described themselves as Hispanic [hazard ratio (HR) 4.8, 95% CI 1.6–14.96] and other race (HR 4.1, 95% CI 1.0–16.3) compared to blacks. Other race included those who were not white, black, or Hispanic. Age and gender were not associated with risk of mortality. In unadjusted bivariable analyses of nondemographic characteristics, alcohol and heroin as drugs of choice (compared with cocaine), persistent homelessness, suicide attempt (ever), drug or alcohol overdose requiring emergency medical attention (ever), and chronic medical illness were each associated with a higher risk of death (Table 1). Better physical health-related quality of life was associated with a lower risk of death. Receipt of primary care was not significantly associated with death (HR 0.85, 95% CI 0.34–2.1). The stepwise procedure resulted in a model that included the following nondemographic risk factors: drug of choice (heroin, alcohol, or cocaine), persistent homelessness, suicide attempt, and chronic medical illness (Table 2). In this multivariable model, heroin (HR 6.9 compared to cocaine, 95% CI 1.6–31.1) and persistent homelessness (HR 2.4, 95% CI 1.1–5.3) were significantly associated with an increased risk of death. To assess confounding by demographic characteristics, a subsequent

regression model was fit that included drug of choice, persistent homelessness (the two significant factors from the stepwise model), and the potential confounders, age, gender, and race. In this adjusted model, heroin as drug of choice remained significantly associated with a higher risk of death (HR 5.4 compared to cocaine, 95% CI 1.1–26.5, $P=0.04$), alcohol as drug of choice was not significantly associated with risk of death (HR 3.0 compared to cocaine, 95% CI 0.6–14.9, $P=0.18$), and the effect of persistent homelessness on risk of death became attenuated and of borderline statistical significance. (HR 2.1, 95% CI 0.97–4.8, $P=0.06$). Age, gender, and race were not associated with risk of mortality ($P>0.15$) in this adjusted model. The probability of death by the end of the follow-up period was 7.1, 1.3, and 17.5% for the substances of choice, alcohol, cocaine, and heroin, respectively; 5.9% for no persistent homelessness and 14.4% for persistent homelessness; 5.7% for no suicide attempt and 16.8% for suicide attempt; and 7.4% for no chronic medical illness and 8.1% for chronic medical illness.

DISCUSSION

Despite the young age of this cohort of men and women with substance dependence, most of whom were not using injection drugs, and who underwent residential detoxification, the short-term mortality rate was high and notably higher than that in the surrounding community. Causes of death could all be related to drug or alcohol dependence. Risk factors identifiable by detailed evaluation at the time of detoxification characterized individuals at even higher risk for death, including heroin as the drug of choice and persistent homelessness. These findings are particularly notable because this cohort had not received primary medical care, and they were at a potential point of entry into the general health system, where they might have risks assessed and addressed. Furthermore, alcohol was the drug of choice for most subjects, thus, adding to the mortality research literature primarily focused on injection drug users. Finally, although there was limited ability to study the impact of health services on mortality, our findings regarding receipt of primary care suggest that such preventive services should be further studied to assess for possible protective effects.

These results expand but are consistent with literature that has reported an increased risk of mortality for people with substance dependence.^{3–8} While mortality rates cannot be directly compared across studies without age or sex adjustment, our results appear to be consistent with other literature reports. A prospective study of mortality among drug users after treatment showed an equally high mortality rate (1.2%), which was six times higher than that for a general, age-matched population.³⁷ A prospective study of mortality after alcohol and drug abuse treatment showed a higher mortality of 2.38% per year, three times that expected in male veterans.³⁸ Moos et al. reported that mortality in treated alcohol-dependent patients was two to five times higher than age- and sex-matched comparison groups.²³ The annual mortality rate for people with opioid abuse in a 12-year follow-up study was 1.4%,⁴ and among subjects with a history of injection drug use in Scotland, the average annual mortality rate was 2.3% over a 21-year period.⁷ These rates are all similar to the 1.7% per year rate in our study and our finding of increased mortality compared with the general population.

Prior studies of substance users have reported causes of death similar to those found in this study. Poisoning, the most common cause of death reported here,

increased in the US by 56% between 1991 and 2001.³⁹ While poisoning accounted for 40.9% of deaths in our study, it was the cause of 22% of the deaths in a 33-year study of heroin users.⁴⁰ A longitudinal intervention study of mortality after drug treatment found the same three leading causes of death: poisoning, trauma, and medical illness.³⁷ Heroin as primary drug of choice is a major focus in the addiction mortality literature because of the high risk of overdose and infectious disease associated with its use.^{4,15,17,18,40,41} Homelessness is another predictor of risk of death for substance-dependent people.^{19–21} Of note, any homelessness was not a significant risk factor in our analyses. Only the more severe “persistent” homelessness was a significant predictor. Our findings also confirm that suicide attempts,^{42–44} chronic medical illness^{13,22,23} and alcohol as drug of choice^{22,45,46} are predictors of mortality in substance-dependent individuals. In this study, neither mental illness nor health literacy was associated with mortality. This observation is not what would be expected based on prior research,^{47,48} and may be because of competing mortality risks in the sample. In addition, we did not assess knowledge of overdose risk or prevention knowledge, which could have been associated with death.

This study relied on rich detailed clinical data obtained by self-report using standardized instruments. Outcomes were ascertained using the well-described National Death Index^{49–51} and supplemented by reports of family and friends provided during active follow-up of the cohort. Nonetheless, several important limitations should be considered. First, it is possible that the death index and the supplemental family reports missed deaths, and the number of deaths in the study was relatively small. As a result, analyses could not consider large numbers of variables simultaneously, and we could not explore interactions or understand possible effects of smaller groups (e.g., individual racial and ethnic groups). Similarly, we may not have been able to identify all predictors of mortality as a result of limited power (e.g., injection drug use, drug overdose, alcohol addiction severity). The absence of a detectable effect of primary care is notable, although one should avoid drawing a conclusion of no mortality benefit. Aside from power limitations and an inability to be confident that we captured all primary care exposures because of limitations in follow-up, we were unable to examine primary care in adjusted analyses over a long-enough period of time to see the effects of high quality preventive and chronic care interventions. However, we were able to identify significant predictors of risk of mortality while adjusting for basic demographic characteristics. Finally, the observational nature of the study limited our ability to draw firm conclusions about causality. This limitation is somewhat tempered by the prospective nature of the study.

Substance dependence is common.¹ Although tobacco use is clearly a substantial contributor to long-term mortality,⁵² in this population of post-detoxification individuals with substance dependence (most of whom smoked cigarettes), relatively short-term mortality is so substantial that it merits consideration for intervention. At least some causes of death in these individuals may be preventable. We have identified characteristics that can be used to identify those at increased risk of mortality after detoxification. Although our findings are consistent with the literature in this area, we add to that literature in a substantial way by reporting on this prospective cohort and by considering a range of clinical characteristics assessed first hand using standardized tools, by including a range of drugs of choice, and by focusing on a common characteristic in substance-dependent adults—lack of regular primary medical care. Given that people who

enter detoxification often have no medical or addiction follow-up care,^{53–57} this is an opportune moment during which people at particularly high risk can be identified and potential interventions can be developed. As the risk for death among detoxification patients overall is elevated, even among those without specific risk factors, attention should be given as to how best to address these individuals' health needs. These findings support arguments for better integrating detoxification and other addictions, psychiatric, and general health care.

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